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=> d his

     (FILE 'REGISTRY' ENTERED AT 12:41:52 ON 01 MAR 2004)
               DEL HIS Y
               ACT PROVISO/A
              ---------
L1          147 SEA FILE=REGISTRY ABB=ON  PLU=ON  EHWSYGLRPG/SQSP
              ---------
               ACT KISH/A
              ---------
L2          152 SEA FILE=REGISTRY ABB=ON  PLU=ON  EHWS[HY]G[WL][YR]PG/SQSP
              ---------
L3            5 S L2 NOT L1

     FILE 'CAPLUS' ENTERED AT 12:44:03 ON 01 MAR 2004
L4            5 S L3

     FILE 'REGISTRY' ENTERED AT 12:44:43 ON 01 MAR 2004
L5            1 S 34346-01-5
L6            2 S 26124-68-5 OR 26009-03-0
L7            1 S 26100-51-6
              E POLYLACTIC ACID/CN
              E POLY LACTIC ACID/CN

     FILE 'CAPLUS' ENTERED AT 12:46:59 ON 01 MAR 2004
L8         1693 S L5
L9         5080 S L6 OR L7
L10        6087 S L8 OR L9
L11         106 S GNRH II
L12         196 S GONADOTROPIN RELEAS? HORMONE (2W) II
L13         114 S GNRH (2W) II
L14         269 S L13 OR L12
L15         269 S L11-L13
L16           1 S L15 AND L10
L17        8570 S GNRH OR GONADOTROPIN RELEAS? (L) HORMONE
L18           8 S L17 AND L10

     FILE 'REGISTRY' ENTERED AT 12:50:58 ON 01 MAR 2004
L19           1 S 9034-40-6

     FILE 'CAPLUS' ENTERED AT 12:51:05 ON 01 MAR 2004
L20       15031 S L19
L21          73 S L20 AND L10
L22       28764 S (TIM? OR CONTROL? OR SUSTAIN? ) (L) RELEAS?
L23          56 S L21 AND L22

     FILE 'REGISTRY' ENTERED AT 12:52:35 ON 01 MAR 2004
               E GONADOTROPIN-RELEASING /CN

     FILE 'CAPLUS' ENTERED AT 12:53:27 ON 01 MAR 2004
L24           8 S L16 OR L18
L25          52 S L23 NOT L24
L26          46 S L25 AND P/DT
               SET SFIELD BI
L27       11711 S GNRH OR GNRHII OR GONADOTROPIN RELEAS? (2W) (FACTOR OR HORMON
L28           0 S L27 AND L26
L29           4 S L23 AND L27

     FILE 'REGISTRY' ENTERED AT 12:58:21 ON 01 MAR 2004
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FILE 'CAPLUS' ENTERED AT 12:58:43 ON 01 MAR 2004

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=> fil caplus
FILE 'CAPLUS' ENTERED AT 12:59:28 ON 01 MAR 2004
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2004 AMERICAN CHEMICAL SOCIETY (ACS)
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FILE COVERS 1907 - 1 Mar 2004  VOL 140 ISS 10
FILE LAST UPDATED: 29 Feb 2004  (20040229/ED)

  This file contains CAS Registry Numbers for easy and accurate
  substance identification.


=> d que l24
L5             1 SEA FILE=REGISTRY ABB=ON  PLU=ON  34346-01-5
L6             2 SEA FILE=REGISTRY ABB=ON  PLU=ON  26124-68-5 OR 26009-03-0
L7             1 SEA FILE=REGISTRY ABB=ON  PLU=ON  26100-51-6
L8          1693 SEA FILE=CAPLUS ABB=ON  PLU=ON  L5
L9          5080 SEA FILE=CAPLUS ABB=ON  PLU=ON  L6 OR L7
L10         6087 SEA FILE=CAPLUS ABB=ON  PLU=ON  L8 OR L9
L11          106 SEA FILE=CAPLUS ABB=ON  PLU=ON  GNRH II/OBI
L12          196 SEA FILE=CAPLUS ABB=ON  PLU=ON  GONADOTROPIN RELEAS? HORMONE/OB
                 I (2W) II/OBI
L13          114 SEA FILE=CAPLUS ABB=ON  PLU=ON  GNRH/OBI (2W) II/OBI
L15          269 SEA FILE=CAPLUS ABB=ON  PLU=ON  (L11 OR L12 OR L13)
L16            1 SEA FILE=CAPLUS ABB=ON  PLU=ON  L15 AND L10
L17         8570 SEA FILE=CAPLUS ABB=ON  PLU=ON  GNRH/OBI OR GONADOTROPIN
                 RELEAS?/OBI (L) HORMONE/OBI
L18            8 SEA FILE=CAPLUS ABB=ON  PLU=ON  L17 AND L10
L24            8 SEA FILE=CAPLUS ABB=ON  PLU=ON  L16 OR L18


=> d que l29
L5             1 SEA FILE=REGISTRY ABB=ON  PLU=ON  34346-01-5
L6             2 SEA FILE=REGISTRY ABB=ON  PLU=ON  26124-68-5 OR 26009-03-0
L7             1 SEA FILE=REGISTRY ABB=ON  PLU=ON  26100-51-6
L8          1693 SEA FILE=CAPLUS ABB=ON  PLU=ON  L5
L9          5080 SEA FILE=CAPLUS ABB=ON  PLU=ON  L6 OR L7
L10         6087 SEA FILE=CAPLUS ABB=ON  PLU=ON  L8 OR L9
L19            1 SEA FILE=REGISTRY ABB=ON  PLU=ON  9034-40-6
L20        15031 SEA FILE=CAPLUS ABB=ON  PLU=ON  L19
L21           73 SEA FILE=CAPLUS ABB=ON  PLU=ON  L20 AND L10
L22        28764 SEA FILE=CAPLUS ABB=ON  PLU=ON  (TIM?/OBI OR CONTROL?/OBI OR
                 SUSTAIN?/OBI ) (L) RELEAS?/OBI
L23           56 SEA FILE=CAPLUS ABB=ON  PLU=ON  L21 AND L22
L27        11711 SEA FILE=CAPLUS ABB=ON  PLU=ON  GNRH OR GNRHII OR GONADOTROPIN
                 RELEAS? (2W) (FACTOR OR HORMONE?)
L29            4 SEA FILE=CAPLUS ABB=ON  PLU=ON  L23 AND L27
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=> d .ca l24 1-8;d .ca l29 1-4

L24 ANSWER 1 OF 8 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:460541 CAPLUS
DOCUMENT NUMBER: 139:41808
TITLE: Manufacture of microcapsules of water-soluble drugs, sustained-release microcapsules, and pharmaceuticals containing the microcapsules
INVENTOR(S): Omura, Tadayoshi; Sekino, Osamu; Okazaki, Junya; Takeyama, Keisuke
PATENT ASSIGNEE(S): Taiyo Pharmaceutical Industry Co., Ltd., Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 6 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 2003171264	A2	20030617	JP 2001-374808	20011207

PRIORITY APPLN. INFO.: JP 2001-374808 20011207

AB In manufacture of microcapsules by (1) preparing W/O emulsions from a solution containing water-soluble drugs as inner aqueous phase and a solution containing polymers as oily phase, (2) dispersing the W/O emulsion in outer aqueous phase, and (3) subjecting the resulting W/O/W emulsion to drying in liquid, water-soluble metal salt compds. are added to aqueous phase used in process after preparation of the W/O/W emulsion, e.g. added to outer aqueous phase or added to aqueous phase for drying in liquid Also claimed are sustained-release microcapsules manufactured by the above method and pharmaceuticals containing the microcapsules. A CH2Cl2 solution of lactic acid-glycolic acid copolymer was mixed with aqueous solution containing polyethylene glycol and leuprorelin acetate (I) to give W/O emulsion. The emulsion was mixed with a portion of aqueous solution containing Zn(OAc)2 and poly(vinyl alc.) to give W/O/W emulsion, which was added to another portion of aqueous solution containing Zn(OAc)2 and poly(vinyl alc.), stirred for 3 h, filtered, mixed with D-mannitol, and freeze-dried to give sustained release microcapsules. Encapsulation rate of I was 99.7% and serum concentration of I after administration of the microcapsules to rats was 4.35 ng/mL after 3 h.

IC ICM A61K009-52
ICS A61K038-04; A61K047-34; A61P005-04; B01J013-12
CC 63-6 (Pharmaceuticals)
IT **Gonadotropin-releasing hormone** receptor
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(agonists; manufacture of sustained-release microcapsules by drying-in-liquid of W/O/W emulsion comprising drug-containing inner aqueous phase, polymer-containing oil phase, and outer aqueous phase using water-soluble metal salts)
IT 58-56-0, Pyridoxine hydrochloride 9034-40-6, Luteinizing hormone-releasing hormone 26023-30-3, Poly[oxy(1-methyl-2-oxo-1,2-ethanediyl)] **26100-51-6**, Poly(lactic acid) **34346-01-5**,

Lactic acid-glycolic acid copolymer 74381-53-6, Leuprorelin acetate
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(manufacture of sustained-release microcapsules by drying-in-liquid of W/O/W emulsion comprising drug-containing inner aqueous phase, polymer-containing oil
phase, and outer aqueous phase using water-soluble metal salts)

L24 ANSWER 2 OF 8 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:133113 CAPLUS
DOCUMENT NUMBER: 138:158871
TITLE: Sustained-release medicines containing angiotensin II antagonists
INVENTOR(S): Kusumoto, Keiji; Hoshino, Tetsuo
PATENT ASSIGNEE(S): Takeda Chemical Industries, Ltd., Japan; Kawamura, Ryu
SOURCE: PCT Int. Appl., 120 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003013609	A1	20030220	WO 2002-JP7862	20020801
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
JP 2003113120	A2	20030418	JP 2002-225671	20020802

PRIORITY APPLN. INFO.: JP 2001-236794 A 20010803
OTHER SOURCE(S): MARPAT 138:158871

AB Disclosed are sustained-release medicines comprising (1) an angiotensin II antagonist combined with (2) one or more drugs selected from among remedies for hypertension, hypoglycemics, remedies for hyperlipemia, antithrombotics, remedies for menopause and anticancer drugs. Using these medicines, remarkably excellent effects can be achieved compared with the case of using each active ingredient alone, which makes it possible to lessen the administration dose and relieve side effects.

IC ICM A61K045-06
ICS A61K031-41; A61K031-4178; A61K031-4184; A61K031-4245; A61K031-519; A61K047-34; A61P009-00; A61P009-12; A61P035-00; A61P043-00
CC 63-6 (Pharmaceuticals)
IT **Gonadotropin-releasing hormone** receptor
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(agonists and antagonists; sustained-release medicines containing angiotensin II antagonists in combination with other drugs for synergism)
IT 50-28-2, Estradiol, biological studies 50-78-2, Aspirin 52-01-7, Spironolactone 58-93-5, Hydrochlorthiazide 133-67-5, Trichlormethiazide 525-66-6, Propranolol 979-32-8, Estradiol valerate 5868-05-3, Niceritrol 9004-10-8, Insulin, biological studies 9005-49-6, Heparin, biological studies 9015-82-1, Angiotensin-converting enzyme 9041-08-1, Enoxaparin sodium 10238-21-8, Glibenclamide 17560-51-9, Metolazone 25812-30-0, Gemfibrozil 26807-65-8, Indapamide

27959-26-8, Cholexamine 28395-03-1, Bumetanide **34346-01-5**, Glycolic acid-lactic acid copolymer 39562-70-4, Nitrendipine 41859-67-0, Bezafibrate 42017-89-0, Fenofibric acid 49562-28-9, Fenofibrate 51384-51-1, Metoprolol 53714-56-0, Leuprorelin 72956-09-3, Carvedilol 74863-84-6, Argatroban 75847-73-3, Enalapril 76547-98-3, Lisinopril 79902-63-9, Simvastatin 81131-70-6, Pravastatin sodium 87333-19-5, Ramipril 87679-37-6, Trandolapril 88150-42-9, Amlodipine 88768-40-5, Cilazapril 89226-50-6, Manidipine 97322-87-7, Troglitazone 105816-04-4, Nateglinide 111902-57-9, Temocapril 112529-15-4, Pioglitazone hydrochloride 113665-84-2, Clopidogrel 114798-26-4, Losartan 129981-36-8, Sampatrilat 133040-01-4, Eprosartan 134523-03-8, Atorvastatin calcium 135038-57-2, Fasidotril 135062-02-1, Repaglinide 137862-53-4, Valsartan 138402-11-6, Irbesartan 139481-59-7, Candesartan 143201-11-0, Cerivastatin sodium 143653-53-6, Abciximab 144689-24-7, Olmesartan 144701-48-4, Telmisartan 145040-37-5, Candesartan cilexetil 147388-92-9 147403-03-0 150375-75-0, Relcovaptan 150683-30-0, Tolvaptan 155141-29-0, Rosiglitazone maleate 167305-00-2, Omapatrilat 168626-94-6, Conivaptan hydrochloride
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(sustained-release medicines containing angiotensin II antagonists in combination with other drugs for synergism)

REFERENCE COUNT: 57 THERE ARE 57 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 3 OF 8 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:849464 CAPLUS
DOCUMENT NUMBER: 137:358129
TITLE: Preventives for postoperative recurrence of premenopausal breast cancer
INVENTOR(S): Igari, Yasutaka; Kusaka, Masami
PATENT ASSIGNEE(S): Takeda Chemical Industries, Ltd., Japan
SOURCE: PCT Int. Appl., 39 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002087616	A1	20021107	WO 2002-JP4071	20020424
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
JP 2003012552	A2	20030115	JP 2002-122734	20020424
EP 1382350	A1	20040121	EP 2002-722741	20020424
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				

PRIORITY APPLN. INFO.: JP 2001-128032 A 20010425
WO 2002-JP4071 W 20020424
OTHER SOURCE(S): MARPAT 137:358129
AB Disclosed are remedies for postoperative recurrence of premenopausal breast cancer containing a GnRH agonist or antagonist which makes it possible

to prevent the postoperative recurrence of premenopausal breast cancer without showing any serious side effects. By using sustained-release microcapsules, the drug effect can be sustained over a long time without frequently administering the drug. Thus, the postoperative recurrence of premenopausal breast cancer can be conveniently prevented over a prolonged period of time. Clin. studies showed that s.c. administration of Lupron Depot was effective to prevent recurrence of the breast cancer.

IC ICM A61K045-00
ICS A61K038-09; A61K009-50; A61K009-52; A61K047-34; A61P005-08; A61P035-00; A61P043-00

CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 1

ST sustained release microcapsule Lupron Depot; premenopausal breast cancer recurrence **GnRH** agonist antagonist

IT Human
Mammary gland, neoplasm
(**GnRH** agonists or antagonists as preventives for postoperative recurrence of premenopausal breast cancer)

IT Antitumor agents
(breast; **GnRH** agonists or antagonists as preventives for postoperative recurrence of premenopausal breast cancer)

IT Drug delivery systems
(microcapsules, sustained-release; sustained-release microcapsules containing **GnRH** agonists or antagonists and biodegradable polymers)

IT Polyesters, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(sustained-release microcapsules containing **GnRH** agonists or antagonists and biodegradable polymers)

IT 9034-40-6, **GnRH**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**GnRH** agonists or antagonists as preventives for postoperative recurrence of premenopausal breast cancer)

IT 53714-56-0 474787-24-1, Leuprolide hydrochloride
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**GnRH** agonists or antagonists as preventives for postoperative recurrence of premenopausal breast cancer)

IT 74381-53-6, Lupron Depot
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**GnRH** agonists or antagonists as preventives for postoperative recurrence of premenopausal breast cancer)

IT **34346-01-5**, Glycolic acid-lactic acid copolymer
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(sustained-release microcapsules containing **GnRH** agonists or antagonists and biodegradable polymers)

REFERENCE COUNT: 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 4 OF 8 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:465844 CAPLUS
DOCUMENT NUMBER: 137:37675
TITLE: Medicinal compositions of nonpeptidyl **gonadotropin-releasing hormone** agonist or antagonist, process for producing the same and use thereof
INVENTOR(S): Suzuki, Hiroshi; Hata, Yoshio
PATENT ASSIGNEE(S): Takeda Chemical Industries, Ltd., Japan
SOURCE: PCT Int. Appl., 93 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002047722	A1	20020620	WO 2001-JP10956	20011214
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2002021139	A5	20020624	AU 2002-21139	20011214
JP 2002326960	A2	20021115	JP 2001-380955	20011214

PRIORITY APPLN. INFO.: JP 2000-382431 A 20001215
WO 2001-JP10956 W 20011214

OTHER SOURCE(S): MARPAT 137:37675

AB Disclosed are medicinal compns. comprising (i) a nonpeptidyl gonadotropin-releasing hormone agonist or antagonist, (ii) an organic acid or its salt, and (iii) a biodegradable polymer or its salt. These compns. can be efficiently produced, suffer from no trouble in quality control and can achieve a stable releasing speed over a long period of time, even in case where the nonpeptidyl GnRH agonist or antagonist is contained in a large amount regardless of the solubility, m.p. or crystallinity thereof. A compound 5-(N-benzyl-N-methylaminomethyl)-1-(2,6-difluorobenzyl)-6-[4-(3-methoxy ureide)phenyl]-3-phenylthieno[2,3-d]pyrimidine-2,4-(1H,3H)-dione was prepared and dissolved in dichloromethane with 3-hydroxy-2-naphthoic acid and polylactic acid. The solution was poured in polyvinyl alc. solution, emulsified, and freeze-dried with mannitol to obtain a microsphere. The microsphere showed controlled-release of the compound when s.c. administered in rats.

IC ICM A61K045-00
ICS A61K031-519; A61K031-4365; A61K009-50; A61K009-52; A61K047-12; A61K047-34; A61P034-00; A61P005-24; A61P035-04; A61P013-08; A61P015-00; A61P017-00; A61P017-14; A61P025-28; A61P015-08; A61P001-00; A61P015-18; C07D495-04

CC 63-6 (Pharmaceuticals)

ST **gonadotropin releasing hormone** agonist antagonist controlled release microsphere

IT Ovulation
(accelerators; medicinal compns. containing nonpeptidic **GnRH** agonists or antagonists, organic acids, and biodegradable polymers)

IT Carboxylic acids, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(aromatic, hydroxy; medicinal compns. containing nonpeptidic **GnRH** agonists or antagonists, organic acids, and biodegradable polymers)

IT Prostate gland, disease
(benign hyperplasia, treatment of; medicinal compns. containing nonpeptidic **GnRH** agonists or antagonists, organic acids, and biodegradable polymers)

IT Polymers, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(biodegradable; medicinal compns. containing nonpeptidic **GnRH** agonists or antagonists, organic acids, and biodegradable polymers)

IT Sex hormones

RL: BSU (Biological study, unclassified); BIOL (Biological study)
(disease related, treatment of; medicinal compns. containing nonpeptidic **GnRH** agonists or antagonists, organic acids, and biodegradable polymers)

IT Uterus, disease
(endometriosis, treatment of; medicinal compns. containing nonpeptidic **GnRH** agonists or antagonists, organic acids, and biodegradable polymers)

IT Hair preparations
(growth stimulants; medicinal compns. containing nonpeptidic **GnRH** agonists or antagonists, organic acids, and biodegradable polymers)

IT Uterus, disease
(hysteromyoma, treatment of; medicinal compns. containing nonpeptidic **GnRH** agonists or antagonists, organic acids, and biodegradable polymers)

IT Drug delivery systems
(injections, sustained release, microsphere; medicinal compns. containing nonpeptidic **GnRH** agonists or antagonists, organic acids, and biodegradable polymers)

IT Intestine, disease
(irritable bowel syndrome, treatment of; medicinal compns. containing nonpeptidic **GnRH** agonists or antagonists, organic acids, and biodegradable polymers)

IT Polyesters, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(lactic acid-based; medicinal compns. containing nonpeptidic **GnRH** agonists or antagonists, organic acids, and biodegradable polymers)

IT Uterus, neoplasm
(leiomyoma, treatment of; medicinal compns. containing nonpeptidic **GnRH** agonists or antagonists, organic acids, and biodegradable polymers)

IT Anti-Alzheimer's agents
Contraceptives
(medicinal compns. containing nonpeptidic **GnRH** agonists or antagonists, organic acids, and biodegradable polymers)

IT Drug delivery systems
(microspheres, controlled-release; medicinal compns. containing nonpeptidic **GnRH** agonists or antagonists, organic acids, and biodegradable polymers)

IT Drug delivery systems
(microspheres, sustained-release, injections; medicinal compns. containing nonpeptidic **GnRH** agonists or antagonists, organic acids, and biodegradable polymers)

IT Ovary, disease
(multilocular ovarian syndrome, treatment of; medicinal compns. containing nonpeptidic **GnRH** agonists or antagonists, organic acids, and biodegradable polymers)

IT Puberty
(precocious puberty, treatment of; medicinal compns. containing nonpeptidic **GnRH** agonists or antagonists, organic acids, and biodegradable polymers)

IT Ovarian cycle
(premenstrual syndrome, treatment of; medicinal compns. containing nonpeptidic **GnRH** agonists or antagonists, organic acids, and biodegradable polymers)

IT Reproduction, animal
(regulation of; medicinal compns. containing nonpeptidic **GnRH** agonists or antagonists, organic acids, and biodegradable polymers)

IT Antitumor agents
(sex hormone-related tumor inhibitor; medicinal compns. containing

nonpeptidic **GnRH** agonists or antagonists, organic acids, and biodegradable polymers)

IT Acne
Alopecia
Alzheimer's disease
Amenorrhea
Dysmenorrhea
Sterility
(treatment of; medicinal compns. containing nonpeptidic **GnRH** agonists or antagonists, organic acids, and biodegradable polymers)

IT 9034-40-6, **Gonadotropin-releasing hormone**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(medicinal compns. containing nonpeptidic **GnRH** agonists or antagonists, organic acids, and biodegradable polymers)

IT 308831-61-0P 392231-14-0P
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(medicinal compns. containing nonpeptidic **GnRH** agonists or antagonists, organic acids, and biodegradable polymers)

IT 69-72-7, Salicylic acid, biological studies 86-48-6, 1-Hydroxy-2-naphthoic acid 92-70-6, 3-Hydroxy-2-naphthoic acid 26023-30-3, Poly[oxy(1-methyl-2-oxo-1,2-ethanediyl)] **26100-51-6**, Polylactic acid **34346-01-5**, Lactic acid-glycolic acid copolymer 174072-31-2 436805-94-6
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(medicinal compns. containing nonpeptidic **GnRH** agonists or antagonists, organic acids, and biodegradable polymers)

IT 103-67-3, Benzylmethylamine 103-71-9, Phenylisocyanate, reactions 105-56-6, Ethyl cyano acetate 128-08-5, N-Bromosuccinimide 697-73-4, 2,6-Difluorobenzylchloride 5332-96-7, 4-Nitrophenylacetone 174072-80-1
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of nonpeptidic **GnRH** agonists or antagonists for microsphere composition containing organic acids and biodegradable polymers)

IT 174069-44-4P 174071-70-6P 174072-63-0P 174072-89-0P 174072-92-5P 174073-19-9P 174073-49-5P 392231-15-1P 392231-16-2P 392231-17-3P 392231-18-4P 392231-97-9P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of nonpeptidic **GnRH** agonists or antagonists for microsphere composition containing organic acids and biodegradable polymers)

REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 5 OF 8 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:383955 CAPLUS
DOCUMENT NUMBER: 133:39671
TITLE: Controlled release formulation comprising **gonadotropin-releasing hormone-II**
INVENTOR(S): Qi, Steve; Akinsanya, Karen; Hayward, Amanda
PATENT ASSIGNEE(S): Ferring Bv, Neth.
SOURCE: PCT Int. Appl., 25 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

WO 2000032218 A1 20000608 WO 1999-GB4045 19991202
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
GB 2344287 A1 20000607 GB 1998-26662 19981203
BR 9915943 A 20010821 BR 1999-15943 19991202
EP 1140133 A1 20011010 EP 1999-958357 19991202
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO
EE 200100293 A 20020815 EE 2001-293 19991202
NZ 511984 A 20021126 NZ 1999-511984 19991202
NO 2001002636 A 20010712 NO 2001-2636 20010529
ZA 2001004530 A 20020604 ZA 2001-4530 20010601
HR 2001000421 A1 20020630 HR 2001-421 20010601
PRIORITY APPLN. INFO.: GB 1998-26662 A 19981203
WO 1999-GB4045 W 19991202

AB A pharmaceutical formulation is disclosed for the controlled release of a therapeutic peptide or a salt thereof, which peptide has the sequence pyroGlu-His-Trp-Ser-Xaa1-Gly-Xaa2-Xaa3-Pro-Gly-NH2 wherein Xaa1 is His or Tyr, Xaa2 is Trp or Leu, and Xaa3 is Tyr or Arg, provided that when Xaa1 is Tyr and Xaa2 is Leu, then Xaa3 is not Arg, and which formulation further comprises a pharmaceutically acceptable biodegradable polymer. The formulation can be used for treating bone and prostate disorders.

IC ICM A61K038-09
ICS A61K047-34
CC 6-3 (General Biochemistry)
Section cross-reference(s): 2
ST bone disease **gonadotropin releasing hormone II** prostate

IT Osteoblast
Osteoclast
Protein sequences
(controlled release formulation comprising **gonadotropin-releasing hormone-II**)

IT Polyesters, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(controlled release formulation comprising **gonadotropin-releasing hormone-II**)

IT Drug delivery systems
(controlled-release; controlled release formulation comprising **gonadotropin-releasing hormone-II**)

IT Carboxylic acids, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(hydroxy, copolymers; controlled release formulation comprising **gonadotropin-releasing hormone-II**)

IT Carboxylic acids, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(hydroxy, polymers; controlled release formulation comprising **gonadotropin-releasing hormone-II**)

IT Encapsulation
(microencapsulation; controlled release formulation comprising

gonadotropin-releasing hormone-II
)

IT 102714-10-3P, **Gonadotropin releasing hormone II**
RL: BAC (Biological activity or effector, except adverse); BPN (Biosynthetic preparation); BSU (Biological study, unclassified); PEP (Physical, engineering or chemical process); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)
(controlled release formulation comprising **gonadotropin-releasing hormone-II**)

IT 91097-16-4P, Luteinizing **hormone**-releasing factor II (chicken)
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PEP (Physical, engineering or chemical process); PNU (Preparation, unclassified); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)
(controlled release formulation comprising **gonadotropin-releasing hormone-II**)

IT 273737-85-2P
RL: PNU (Preparation, unclassified); RCT (Reactant); PREP (Preparation); RACT (Reactant or reagent)
(controlled release formulation comprising **gonadotropin-releasing hormone-II**)

IT **26009-03-0**, Polyglycolic acid 26023-30-3, Poly[oxy(1-methyl-2-oxo-1,2-ethanediyl)] **26100-51-6**, Polylactic acid **26124-68-5**, Polyglycolic acid **34346-01-5**, Glycolic acid-lactic acid copolymer
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(controlled release formulation comprising **gonadotropin-releasing hormone-II**)

IT 220159-23-9 273952-33-3, 1: PN: WO0032218 SEQID: 1 unclaimed DNA 273952-34-4, 2: PN: WO0032218 SEQID: 2 unclaimed DNA 273952-35-5, 3: PN: WO0032218 SEQID: 3 unclaimed DNA
RL: PRP (Properties)
(unclaimed nucleotide sequence; controlled release formulation comprising **gonadotropin-releasing hormone-II**)

IT 274262-43-0
RL: PRP (Properties)
(unclaimed protein sequence; controlled release formulation comprising **gonadotropin-releasing hormone-II**
)

IT 60556-70-9 261962-20-3
RL: PRP (Properties)
(unclaimed sequence; controlled release formulation comprising **gonadotropin-releasing hormone-II**
)

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 6 OF 8 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1997:359790 CAPLUS
DOCUMENT NUMBER: 127:55785
TITLE: Small-size microcapsules for long-term **GnRH** agonist administration
AUTHOR(S): Ogawa, Y.
CORPORATE SOURCE: UK
SOURCE: Treatment with GnRH Analogs: Controversies and Perspectives, Proceedings of a Satellite Symposium of the 15th World Congress on Fertility and Sterility,

Bologna, Sept. 15-16, 1995 (1996), Meeting Date 1995, 47-52. Editor(s): Filicori, Marco; Flamigni, Carlo. Parthenon Publishing: London, UK.
CODEN: 64KRAZ
DOCUMENT TYPE: Conference
LANGUAGE: English

AB Microcapsules containing 10% leuprorelin were prepared by using poly(glycolic-co-lactic acid) in an in-water drying procedure. The mean diameter of the capsules was 20 μm. The amount of the drug released initially depended on the particle size of the microcapsules and the drug solubility

CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 2

ST **GnRH** agonist microcapsule; leuprorelin microcapsule polyester

IT Uterus, disease
(endometriosis; small-size microcapsules for long-term **GnRH** agonist administration)

IT Polyesters, biological studies
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(hydroxycarboxylic acid-based; small-size microcapsules for long-term **GnRH** agonist administration)

IT Drug delivery systems
(microcapsules; small-size microcapsules for long-term **GnRH** agonist administration)

IT Dissolution rate
Particle size distribution
Polymer degradation
(small-size microcapsules for long-term **GnRH** agonist administration)

IT **Gonadotropin-releasing hormone** receptor
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(small-size microcapsules for long-term **GnRH** agonist administration)

IT 53714-56-0, Leuprorelin
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(small-size microcapsules for long-term **GnRH** agonist administration)

IT **34346-01-5P**, Glycolic acid-lactic acid copolymer
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(small-size microcapsules for long-term **GnRH** agonist administration)

IT 74381-53-6, Leuprorelin acetate
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(small-size microcapsules for long-term **GnRH** agonist administration)

L24 ANSWER 7 OF 8 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1992:158746 CAPLUS
DOCUMENT NUMBER: 116:158746
TITLE: Effects of TAP-144-SR, a sustained-release formulation of a potent **GnRH** agonist, on experimental endometriosis in the rat
AUTHOR(S): Sudo, Katsuichi; Shiota, Kunio; Masaki, Tsuneo; Fujita, Takeshi
CORPORATE SOURCE: Biol. Res. Lab., Takeda Chem. Ind., Ltd., Osaka, 532, Japan

SOURCE: Endocrinologia Japonica (1991), 38(1), 39-45
CODEN: ECJPAE; ISSN: 0013-7219
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A new, simple exptl. endometriosis model was established by auto-transplanting endometrial tissue fragments beneath kidney capsules in female rats. The transplanted endometrial tissue grew well, forming a fluid-filled cyst, which reached maximal size 2 to 3 wk after transplantation. The growth and maintenance of the transplants was dependent on the ovary: ovariectomy induced regression of well grown transplants. The therapeutic effects of TAP-144-SR [biodegradable microcapsules of copoly(DL-lactic/glycolic acid) copolymer containing a potent GnRH agonist, TAP-144 (D-Leu6-[des-Gly10-NH2]-GnRH ethylamide, leuprolide acetate) were studied with this rat endometriosis model. A single s.c. injection of TAP-144-SR (corresponding to 1, 10 or 100 μg/kg/day of TAP-144), suppressed the growth of the transplanted endometrial tissues and uterine weight in a dose-dependent manner. At 100 μg/kg/day, the suppressive effect was more marked in rats given TAP-144-SR than in those given TAP-144 solution The extent of suppression was comparable to that caused by ovariectomy. Serum and pituitary concns. of LH and FSH were also reduced more markedly by the administration of TAP-144-SR than by TAP-144 solution From these results, the present endometriosis model was found to be useful for the evaluation of compds. with potential therapeutic activity. The sustained-release formulation of TAP-144 seems to be beneficial over its solution in terms ob both convenience and efficiency for therapy of patients with endometriosis.

CC 63-5 (Pharmaceuticals)
Section cross-reference(s): 2

IT **34346-01-5**, Glycolic acid-DL-lactic acid copolymer
RL: BIOL (Biological study)
(microspheres, sustained-release biodegradable, leuprolide acetate therapeutic efficacy from, in rat endometriosis model)

L24 ANSWER 8 OF 8 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1991:49580 CAPLUS
DOCUMENT NUMBER: 114:49580
TITLE: Sustained-release compositions containing **gonadotropin-releasing hormone (GnRH)**, luteinizing **hormone**-releasing **hormone** (LHRH) or derivatives thereof, and their use
INVENTOR(S): Zohar, Jonathan
PATENT ASSIGNEE(S): Israel Oceanographic and Limnological Research Ltd., Israel
SOURCE: Eur. Pat. Appl., 10 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 368000	A1	19900516	EP 1989-118753	19891009
EP 368000	B1	19980107		
R: AT, BE, CH, DE, ES, FR, GB, GR, IT, LI, LU, NL, SE				
CA 1338466	A1	19960723	CA 1989-615059	19890929
US 5288705	A	19940222	US 1989-417772	19891006
NO 8904026	A	19900411	NO 1989-4026	19891009
AT 161714	E	19980115	AT 1989-118753	19891009

ES 2114851 T3 19980616 ES 1989-118753 19891009
PRIORITY APPLN. INFO.: IL 1988-87982 19881010
AB A composition for the manipulation of reproduction in fish comprises an effective amount of GnRH, LHRH, or their analogs or salts, embedded in a sustained-release biocompatible polymer-based matrix. Thus, female seabream (Sporus aurata) with an implant of GnRH analog in poly(glycolic acid-lactic acid) (150 μg GnRH analog/fish), maintained elevated plasma levels of gonadotropin >10 days, and displayed 80% spawning activity vs. 25% for fish receiving the same analog in saline.
IC ICM A61K009-20
ICS A61K009-26; A61K037-43
CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 1, 12
ST fish reprodn control sustained release pharmaceutical; **gonadotropin releasing hormone** sustained release; LH releasing **hormone** sustained release
IT 24937-78-8, Ethylene-vinyl acetate copolymer **34346-01-5**, Glycolic acid-lactic acid copolymer
RL: BIOL (Biological study)
(sustained-release pharmaceuticals containing reproduction hormones and, for fish reproduction control)

L29 ANSWER 1 OF 4 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:460541 CAPLUS
DOCUMENT NUMBER: 139:41808
TITLE: Manufacture of microcapsules of water-soluble drugs, **sustained-release** microcapsules, and pharmaceuticals containing the microcapsules
INVENTOR(S): Omura, Tadayoshi; Sekino, Osamu; Okazaki, Junya; Takeyama, Keisuke
PATENT ASSIGNEE(S): Taiyo Pharmaceutical Industry Co., Ltd., Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 6 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 2003171264	A2	20030617	JP 2001-374808	20011207

PRIORITY APPLN. INFO.: JP 2001-374808 20011207
AB In manufacture of microcapsules by (1) preparing W/O emulsions from a solution containing water-soluble drugs as inner aqueous phase and a solution containing polymers as oily phase, (2) dispersing the W/O emulsion in outer aqueous phase, and (3) subjecting the resulting W/O/W emulsion to drying in liquid, water-soluble metal salt compds. are added to aqueous phase used in process after preparation of the W/O/W emulsion, e.g. added to outer aqueous phase or added to aqueous phase for drying in liquid Also claimed are sustained-release microcapsules manufactured by the above method and pharmaceuticals containing the microcapsules.
A CH2Cl2 solution of lactic acid-glycolic acid copolymer was mixed with aqueous solution containing polyethylene glycol and leuprorelin acetate (I) to give W/O

emulsion. The emulsion was mixed with a portion of aqueous solution containing Zn(OAc)2 and poly(vinyl alc.) to give W/O/W emulsion, which was added to another portion of aqueous solution containing Zn(OAc)2 and poly(vinyl alc.), stirred for 3 h, filtered, mixed with D-mannitol, and freeze-dried to give sustained release microcapsules. Encapsulation rate of I was 99.7% and serum concentration of I after administration of the microcapsules to rats was 4.35 ng/mL after 3 h.

IC ICM A61K009-52
ICS A61K038-04; A61K047-34; A61P005-04; B01J013-12

CC 63-6 (Pharmaceuticals)

ST **sustained release** water sol drug microcapsule WOW emulsion drying; leuprorelin **sustained release** microcapsule outer aq phases zinc acetate

IT **Gonadotropin-releasing hormone** receptor
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(agonists; manufacture of **sustained-release** microcapsules by drying-in-liquid of W/O/W emulsion comprising drug-containing inner aqueous phase, polymer-containing oil phase, and outer aqueous phase using water-soluble metal salts)

IT Alkaline earth salts
Transition metal salts
RL: MOA (Modifier or additive use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(manufacture of **sustained-release** microcapsules by drying-in-liquid of W/O/W emulsion comprising drug-containing inner aqueous phase, polymer-containing oil phase, and outer aqueous phase using water-soluble metal salts)

IT Drug delivery systems
(microcapsules, **sustained-release**; manufacture of **sustained-release** microcapsules by drying-in-liquid of W/O/W emulsion comprising drug-containing inner aqueous phase, polymer-containing oil phase, and outer aqueous phase using water-soluble metal salts)

IT 557-34-6, Zinc acetate
RL: MOA (Modifier or additive use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(manufacture of **sustained-release** microcapsules by drying-in-liquid of W/O/W emulsion comprising drug-containing inner aqueous phase, polymer-containing oil phase, and outer aqueous phase using water-soluble metal salts)

IT 58-56-0, Pyridoxine hydrochloride **9034-40-6**, Luteinizing hormone-**releasing** hormone 26023-30-3, Poly[oxy(1-methyl-2-oxo-1,2-ethanediyl)] **26100-51-6**, Poly(lactic acid) **34346-01-5**, Lactic acid-glycolic acid copolymer 74381-53-6, Leuprorelin acetate
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(manufacture of **sustained-release** microcapsules by drying-in-liquid of W/O/W emulsion comprising drug-containing inner aqueous phase, polymer-containing oil phase, and outer aqueous phase using water-soluble metal salts)

L29 ANSWER 2 OF 4 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:849464 CAPLUS
DOCUMENT NUMBER: 137:358129
TITLE: Preventives for postoperative recurrence of

premenopausal breast cancer
INVENTOR(S): Igari, Yasutaka; Kusaka, Masami
PATENT ASSIGNEE(S): Takeda Chemical Industries, Ltd., Japan
SOURCE: PCT Int. Appl., 39 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002087616	A1	20021107	WO 2002-JP4071	20020424
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
JP 2003012552	A2	20030115	JP 2002-122734	20020424
EP 1382350	A1	20040121	EP 2002-722741	20020424
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				

PRIORITY APPLN. INFO.: JP 2001-128032 A 20010425
WO 2002-JP4071 W 20020424
OTHER SOURCE(S): MARPAT 137:358129

AB Disclosed are remedies for postoperative recurrence of premenopausal breast cancer containing a **GnRH** agonist or antagonist which makes it possible to prevent the postoperative recurrence of premenopausal breast cancer without showing any serious side effects. By using sustained-release microcapsules, the drug effect can be sustained over a long time without frequently administering the drug. Thus, the postoperative recurrence of premenopausal breast cancer can be conveniently prevented over a prolonged period of time. Clin. studies showed that s.c. administration of Lupron Depot was effective to prevent recurrence of the breast cancer.

IC ICM A61K045-00
ICS A61K038-09; A61K009-50; A61K009-52; A61K047-34; A61P005-08; A61P035-00; A61P043-00
CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 1
ST **sustained release** microcapsule Lupron Depot; premenopausal breast cancer recurrence **GnRH** agonist antagonist
IT Human
Mammary gland, neoplasm
(**GnRH** agonists or antagonists as preventives for postoperative recurrence of premenopausal breast cancer)
IT Antitumor agents
(breast; **GnRH** agonists or antagonists as preventives for postoperative recurrence of premenopausal breast cancer)
IT Drug delivery systems
(microcapsules, **sustained-release**; **sustained-release** microcapsules containing **GnRH** agonists or antagonists and biodegradable polymers)
IT Polyesters, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**sustained-release** microcapsules containing

GnRH agonists or antagonists and biodegradable polymers)
IT **9034-40-6, GnRH**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**GnRH** agonists or antagonists as preventives for postoperative recurrence of premenopausal breast cancer)
IT 53714-56-0 474787-24-1, Leuprolide hydrochloride
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**GnRH** agonists or antagonists as preventives for postoperative recurrence of premenopausal breast cancer)
IT 74381-53-6, Lupron Depot
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**GnRH** agonists or antagonists as preventives for postoperative recurrence of premenopausal breast cancer)
IT **34346-01-5**, Glycolic acid-lactic acid copolymer
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**sustained-release** microcapsules containing **GnRH** agonists or antagonists and biodegradable polymers)
REFERENCE COUNT: 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L29 ANSWER 3 OF 4 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:465844 CAPLUS
DOCUMENT NUMBER: 137:37675
TITLE: Medicinal compositions of nonpeptidyl **gonadotropin-releasing hormone** agonist or antagonist, process for producing the same and use thereof
INVENTOR(S): Suzuki, Hiroshi; Hata, Yoshio
PATENT ASSIGNEE(S): Takeda Chemical Industries, Ltd., Japan
SOURCE: PCT Int. Appl., 93 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002047722	A1	20020620	WO 2001-JP10956	20011214
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2002021139	A5	20020624	AU 2002-21139	20011214
JP 2002326960	A2	20021115	JP 2001-380955	20011214

PRIORITY APPLN. INFO.: JP 2000-382431 A 20001215
WO 2001-JP10956 W 20011214
OTHER SOURCE(S): MARPAT 137:37675
AB Disclosed are medicinal compns. comprising (i) a nonpeptidyl **gonadotropin-releasing hormone** agonist or antagonist, (ii) an organic acid or its salt, and (iii) a biodegradable polymer or its salt. These compns. can be efficiently produced, suffer from no trouble in quality control and can achieve a stable releasing speed over a long period of time, even in case where the nonpeptidyl

GnRH agonist or antagonist is contained in a large amount regardless of the solubility, m.p. or crystallinity thereof. A compound 5-(N-benzyl-N-methylaminomethyl)-1-(2,6-difluorobenzyl)-6-[4-(3-methoxy ureide)phenyl]-3-phenylthieno[2,3-d]pyrimidine-2,4-(1H,3H)-dione was prepared and dissolved in dichloromethane with 3-hydroxy-2-naphthoic acid and polylactic acid. The solution was poured in polyvinyl alc. solution, emulsified, and freeze-dried with mannitol to obtain a microsphere. The microsphere showed controlled-release of the compound when s.c. administered in rats.

IC ICM A61K045-00
ICS A61K031-519; A61K031-4365; A61K009-50; A61K009-52; A61K047-12; A61K047-34; A61P034-00; A61P005-24; A61P035-04; A61P013-08; A61P015-00; A61P017-00; A61P017-14; A61P025-28; A61P015-08; A61P001-00; A61P015-18; C07D495-04

CC 63-6 (Pharmaceuticals)

ST **gonadotropin releasing hormone** agonist antagonist **controlled release** microsphere

IT Ovulation
(accelerators; medicinal compns. containing nonpeptidic **GnRH** agonists or antagonists, organic acids, and biodegradable polymers)

IT Carboxylic acids, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(aromatic, hydroxy; medicinal compns. containing nonpeptidic **GnRH** agonists or antagonists, organic acids, and biodegradable polymers)

IT Prostate gland, disease
(benign hyperplasia, treatment of; medicinal compns. containing nonpeptidic **GnRH** agonists or antagonists, organic acids, and biodegradable polymers)

IT Polymers, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(biodegradable; medicinal compns. containing nonpeptidic **GnRH** agonists or antagonists, organic acids, and biodegradable polymers)

IT Sex hormones
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(disease related, treatment of; medicinal compns. containing nonpeptidic **GnRH** agonists or antagonists, organic acids, and biodegradable polymers)

IT Uterus, disease
(endometriosis, treatment of; medicinal compns. containing nonpeptidic **GnRH** agonists or antagonists, organic acids, and biodegradable polymers)

IT Hair preparations
(growth stimulants; medicinal compns. containing nonpeptidic **GnRH** agonists or antagonists, organic acids, and biodegradable polymers)

IT Uterus, disease
(hysteromyoma, treatment of; medicinal compns. containing nonpeptidic **GnRH** agonists or antagonists, organic acids, and biodegradable polymers)

IT Drug delivery systems
(injections, **sustained release**, microsphere; medicinal compns. containing nonpeptidic **GnRH** agonists or antagonists, organic acids, and biodegradable polymers)

IT Intestine, disease
(irritable bowel syndrome, treatment of; medicinal compns. containing nonpeptidic **GnRH** agonists or antagonists, organic acids, and biodegradable polymers)

IT Polyesters, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(lactic acid-based; medicinal compns. containing nonpeptidic **GnRH** agonists or antagonists, organic acids, and biodegradable polymers)

IT Uterus, neoplasm
(leiomyoma, treatment of; medicinal compns. containing nonpeptidic **GnRH** agonists or antagonists, organic acids, and biodegradable polymers)
IT Anti-Alzheimer's agents
Contraceptives
(medicinal compns. containing nonpeptidic **GnRH** agonists or antagonists, organic acids, and biodegradable polymers)
IT Drug delivery systems
(microspheres, **controlled-release**; medicinal compns. containing nonpeptidic **GnRH** agonists or antagonists, organic acids, and biodegradable polymers)
IT Drug delivery systems
(microspheres, **sustained-release**, injections; medicinal compns. containing nonpeptidic **GnRH** agonists or antagonists, organic acids, and biodegradable polymers)
IT Ovary, disease
(multilocular ovarian syndrome, treatment of; medicinal compns. containing nonpeptidic **GnRH** agonists or antagonists, organic acids, and biodegradable polymers)
IT Puberty
(precocious puberty, treatment of; medicinal compns. containing nonpeptidic **GnRH** agonists or antagonists, organic acids, and biodegradable polymers)
IT Ovarian cycle
(premenstrual syndrome, treatment of; medicinal compns. containing nonpeptidic **GnRH** agonists or antagonists, organic acids, and biodegradable polymers)
IT Reproduction, animal
(regulation of; medicinal compns. containing nonpeptidic **GnRH** agonists or antagonists, organic acids, and biodegradable polymers)
IT Antitumor agents
(sex hormone-related tumor inhibitor; medicinal compns. containing nonpeptidic **GnRH** agonists or antagonists, organic acids, and biodegradable polymers)
IT Acne
Alopecia
Alzheimer's disease
Amenorrhea
Dysmenorrhea
Sterility
(treatment of; medicinal compns. containing nonpeptidic **GnRH** agonists or antagonists, organic acids, and biodegradable polymers)
IT **9034-40-6, Gonadotropin-releasing hormone**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(medicinal compns. containing nonpeptidic **GnRH** agonists or antagonists, organic acids, and biodegradable polymers)
IT 308831-61-0P 392231-14-0P
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(medicinal compns. containing nonpeptidic **GnRH** agonists or antagonists, organic acids, and biodegradable polymers)
IT 69-72-7, Salicylic acid, biological studies 86-48-6, 1-Hydroxy-2-naphthoic acid 92-70-6, 3-Hydroxy-2-naphthoic acid 26023-30-3, Poly[oxy(1-methyl-2-oxo-1,2-ethanediyl)] **26100-51-6**, Polylactic acid **34346-01-5**, Lactic acid-glycolic acid copolymer 174072-31-2 436805-94-6
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(medicinal compns. containing nonpeptidic **GnRH** agonists or

antagonists, organic acids, and biodegradable polymers)
IT 103-67-3, Benzylmethylamine 103-71-9, Phenylisocyanate, reactions
105-56-6, Ethyl cyano acetate 128-08-5, N-Bromosuccinimide 697-73-4,
2,6-Difluorobenzylchloride 5332-96-7, 4-Nitrophenylacetone 174072-80-1
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of nonpeptidic **GnRH** agonists or antagonists for
microsphere composition containing organic acids and biodegradable polymers)
IT 174069-44-4P 174071-70-6P 174072-63-0P 174072-89-0P 174072-92-5P
174073-19-9P 174073-49-5P 392231-15-1P 392231-16-2P 392231-17-3P
392231-18-4P 392231-97-9P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT
(Reactant or reagent)
(preparation of nonpeptidic **GnRH** agonists or antagonists for
microsphere composition containing organic acids and biodegradable polymers)
REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L29 ANSWER 4 OF 4 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1991:49580 CAPLUS
DOCUMENT NUMBER: 114:49580
TITLE: **Sustained-release** compositions containing **gonadotropin-releasing hormone** (**GnRH**), luteinizing hormone-**releasing** hormone (LHRH) or derivatives thereof, and their use
INVENTOR(S): Zohar, Jonathan
PATENT ASSIGNEE(S): Israel Oceanographic and Limnological Research Ltd., Israel
SOURCE: Eur. Pat. Appl., 10 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 368000	A1	19900516	EP 1989-118753	19891009
EP 368000	B1	19980107		
R: AT, BE, CH, DE, ES, FR, GB, GR, IT, LI, LU, NL, SE				
CA 1338466	A1	19960723	CA 1989-615059	19890929
US 5288705	A	19940222	US 1989-417772	19891006
NO 8904026	A	19900411	NO 1989-4026	19891009
AT 161714	E	19980115	AT 1989-118753	19891009
ES 2114851	T3	19980616	ES 1989-118753	19891009

PRIORITY APPLN. INFO.: IL 1988-87982 19881010
AB A composition for the manipulation of reproduction in fish comprises an effective
amount of **GnRH**, LHRH, or their analogs or salts, embedded in a sustained-release biocompatible polymer-based matrix. Thus, female seabream (Sporus aurata) with an implant of **GnRH** analog in poly(glycolic acid-lactic acid) (150 μg **GnRH** analog/fish), maintained elevated plasma levels of gonadotropin >10 days, and displayed 80% spawning activity vs. 25% for fish receiving the same analog in saline.
IC ICM A61K009-20
ICS A61K009-26; A61K037-43
CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 1, 12
ST fish reprodn **control sustained release**

pharmaceutical; **gonadotropin releasing hormone sustained release**; LH **releasing** hormone **sustained release**

IT Gonadotropins
RL: BIOL (Biological study)
(analogs, **sustained-release** pharmaceuticals containing, for reproduction **control** in fish)

IT Reproduction
(manipulation of, in fish, **sustained-release** hormones for)

IT Dicentrarchus labrax
Salmo gairdneri
Sparus auratus
(reproduction **control** in, **sustained-release** hormone implants for)

IT Fish
(reproduction **control** in, **sustained-release** hormones for)

IT Biopolymers
Polyesters, biological studies
Polysaccharides, biological studies
Proteins, biological studies
Rubber, silicone, biological studies
RL: BIOL (Biological study)
(**sustained-release** pharmaceuticals containing reproduction hormones and, for fish reproduction **control**)

IT Neurotransmitter antagonists
(dopaminergic, **sustained-release** pharmaceutical containing reproduction hormones and, for fish reproduction **control**)

IT Pharmaceutical dosage forms
(implants, **sustained-release**, reproduction hormones in, for fish reproduction **control**)

IT Anhydrides
RL: BIOL (Biological study)
(poly-, **sustained-release** pharmaceuticals containing reproduction hormones and, for fish reproduction **control**)

IT Reproduction
(spawning, manipulation of, in fish, **sustained-release** hormones for)

IT Pharmaceutical dosage forms
(**sustained-release**, reproduction hormones in, for fish reproduction **control**)

IT 24937-78-8, Ethylene-vinyl acetate copolymer **34346-01-5**, Glycolic acid-lactic acid copolymer
RL: BIOL (Biological study)
(**sustained-release** pharmaceuticals containing reproduction hormones and, for fish reproduction **control**)

IT **9034-40-6**, Luteinizing hormone-**releasing** hormone **9034-40-6D**, Luteinizing hormone-**releasing** factor, analogs
RL: BIOL (Biological study)
(**sustained-release** pharmaceuticals containing, for reproduction **control** in fish)

=>

=> fil wpids
FILE 'WPIDS' ENTERED AT 13:10:53 ON 01 MAR 2004

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FILE LAST UPDATED:          26 FEB 2004      <20040226/UP>
MOST RECENT DERWENT UPDATE:     200414        <200414/DW>
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    DERWENT UPDATE 200403.
    THE TIME RANGE CODE WILL ALSO CHANGE FROM 018 TO 2004.
    SDIS USING THE TIME RANGE CODE WILL NEED TO BE UPDATED.
    FOR FURTHER DETAILS: http://thomsonderwent.com/chem/polymers/ <<<


=> d que l9
L1            11 SEA FILE=WPIDS ABB=ON  PLU=ON  GNRH  (2W) II OR GNRHII
L2           329 SEA FILE=WPIDS ABB=ON  PLU=ON  GONADOTROPIN (2W) RELEAS? (2W)
                 (FACTOR OR HORMONE)
L3          3210 SEA FILE=WPIDS ABB=ON  PLU=ON  POLY (3A) (GLYCOLIC  OR LACTIC)
                  OR POLYGLYCOLIC OR POLYLACTIC
L4           157 SEA FILE=WPIDS ABB=ON  PLU=ON  POLY (3A) (GLYCOLATE  OR
                 LACTATE)  OR POLYGLYCOLATE OR POLYLACTATE
L5          3337 SEA FILE=WPIDS ABB=ON  PLU=ON  L3 OR L4
L6          1052 SEA FILE=WPIDS ABB=ON  PLU=ON  (LACTIC OR LACTATE ) (S)
                 (GLYCOLATE OR GLYCOLIC) (S) ?POLYMER?
L7          3887 SEA FILE=WPIDS ABB=ON  PLU=ON  L5 OR L6
L8           330 SEA FILE=WPIDS ABB=ON  PLU=ON  L1 OR L2
L9             3 SEA FILE=WPIDS ABB=ON  PLU=ON  L8 AND L7


=> d que l14
L1            11 SEA FILE=WPIDS ABB=ON  PLU=ON  GNRH  (2W) II OR GNRHII
L2           329 SEA FILE=WPIDS ABB=ON  PLU=ON  GONADOTROPIN (2W) RELEAS? (2W)
                 (FACTOR OR HORMONE)
L3          3210 SEA FILE=WPIDS ABB=ON  PLU=ON  POLY (3A) (GLYCOLIC  OR LACTIC)
                  OR POLYGLYCOLIC OR POLYLACTIC
L4           157 SEA FILE=WPIDS ABB=ON  PLU=ON  POLY (3A) (GLYCOLATE  OR
                 LACTATE)  OR POLYGLYCOLATE OR POLYLACTATE
L5          3337 SEA FILE=WPIDS ABB=ON  PLU=ON  L3 OR L4
L6          1052 SEA FILE=WPIDS ABB=ON  PLU=ON  (LACTIC OR LACTATE ) (S)
                 (GLYCOLATE OR GLYCOLIC) (S) ?POLYMER?
L7          3887 SEA FILE=WPIDS ABB=ON  PLU=ON  L5 OR L6
L8           330 SEA FILE=WPIDS ABB=ON  PLU=ON  L1 OR L2
L9             3 SEA FILE=WPIDS ABB=ON  PLU=ON  L8 AND L7
L10         1871 SEA FILE=WPIDS ABB=ON  PLU=ON  RELEASING (2W) (PEPTIDE OR
                 HORMONE OR FACTOR)
L11           46 SEA FILE=WPIDS ABB=ON  PLU=ON  L10 AND L7
L12        36010 SEA FILE=WPIDS ABB=ON  PLU=ON  (SUSTAIN? OR CONTROL? OR TIME?)
                 (5A) (RELEAS?)
L13           27 SEA FILE=WPIDS ABB=ON  PLU=ON  L11 AND L12
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L14 25 SEA FILE=WPIDS ABB=ON PLU=ON L13 NOT L9

=> d .wp l9 1-3;d .wp l14 1-25

L9 ANSWER 1 OF 3 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
AN 2002-599485 [64] WPIDS
DNC C2002-169315
TI Composition for administering nonpeptidic **gonadotropin-releasing hormone** agonist or antagonist, comprises organic acid and biodegradable polymer.
DC A96 B02
IN HATA, Y; SUZUKI, H
PA (TAKE) TAKEDA CHEM IND LTD
CYC 99
PI WO 2002047722 A1 20020620 (200264)* JA 93p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VN YU ZA ZM ZW
AU 2002021139 A 20020624 (200267)
JP 2002326960 A 20021115 (200306) 38p
ADT WO 2002047722 A1 WO 2001-JP10956 20011214; AU 2002021139 A AU 2002-21139 20011214; JP 2002326960 A JP 2001-380955 20011214
FDT AU 2002021139 A Based on WO 2002047722
PRAI JP 2000-382431 20001215
AB WO 200247722 A UPAB: 20021007
NOVELTY - Composition is claimed comprising:
(i) a nonpeptidic **gonadotropin-releasing hormone** agonist or antagonist;
(ii) an organic acid or its salt; and
(iii) a biodegradable polymer or its salt.
ACTIVITY - Cytostatic; Osteopathic; Gynecological; Neuroprotective; Nootropic; Antiinflammatory.
Isopropyl 3-(N-methyl-N-benzylaminomethyl)-4,7-dihydro-7-(2,6-difluorobenzyl)-2-(4-(3-methoxyureido)phenyl)-4-oxathieno(2,3-b)pyrimidine-5-carboxylate (Ia) (720 mg), 3-hydroxy-2-naphthoic acid (210 mg) and **polylactic** acid (weight average molecular weight = 9800; 270 mg) were mixed in dichloromethane (1.2 ml). The solvent was removed and polyvinylalcohol (0.1 w/v%; 300 ml) was added. The mixture was homogenized to give an oil in water emulsion and centrifuged (2500 rpm) to give microspheres. The microspheres were washed with water (300 ml), mixed with mannitol (120 mg) and dried to give 900 mg of microspheres. The microspheres (25 mg) were injected into SD rats and the amount of activity remaining after 1 day, 1 week, 3 week or 5 weeks was 94, 65, 24 and 19% respectively.
MECHANISM OF ACTION - None given.
USE - For administering nonpeptidic **gonadotropin-releasing hormone** agonists or antagonists useful for treating e.g. cancer, osteoporosis, prostatic hypertrophy, mastopathy, endometriosis, Alzheimer's disease and irritable bowel syndrome.
ADVANTAGE - Are efficiently produced, contain reduced amount of organic solvent and give a stable release rate over a long period of time even with large amounts of agonist or antagonist and regardless of the solubility, melting point or crystallinity.
Dwg.0/0
TECH UPTX: 20021007
TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preferred Composition: Composition

comprises:
(i) at least 15 weight % of a nonpeptidic **gonadotropin-releasing hormone** agonist or antagonist having a molecular weight of 1000 or less (preferably a thienopyrimidinedione compound of formula (I) or its salt);
(ii) salicylic acid, 1-hydroxy-2-naphthoic acid, 3-hydroxy-2-naphthoic acid or pamic acid; and
(iii) an alpha-hydroxycarboxylic acid **copolymer** (preferably **lactic** acid/**glycolic** acid **copolymer** having a mol ratio of 100/0-40-60 and an weight average molecular weight of 300-1000).
R1, R2 = H, OH, OA, COA or optionally substituted A;
A = 1-4C alkyl;
R3 = H, halo, OH or OA; or
R3+R3 = 1-4C alkylenedioxy;
R4 = H or A;
R6 = optionally substituted A or CH2Ph;
Ph = phenyl o-substituted by R5;
R5 = H; or
R4+R4 = ring; and
n = 0-5.

L9 ANSWER 2 OF 3 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
AN 2002-557416 [59] WPIDS
DNC C2002-158124
TI New formulation useful for controlled release of bioactive molecules e.g. proteins comprises biodegradable polymer in combination with conjugate of bioactive molecule and hydrophilic polymer.
DC A96 B05 B07 D16
IN HINDS, K; LEWIS, D; SCHMIDT, P
PA (PRPH-N) PR PHARM INC; (HIND-I) HINDS K; (LEWI-I) LEWIS D; (SCHM-I) SCHMIDT P
CYC 98
PI WO 2002036169 A2 20020510 (200259)* EN 24p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
AU 2002020002 A 20020515 (200259)
US 2002155158 A1 20021024 (200273)
EP 1353701 A2 20031022 (200370) EN
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR
ADT WO 2002036169 A2 WO 2001-US45154 20011031; AU 2002020002 A AU 2002-20002 20011031; US 2002155158 A1 Provisional US 2000-244499P 20001031, US 2001-999820 20011031; EP 1353701 A2 EP 2001-992587 20011031, WO 2001-US45154 20011031
FDT AU 2002020002 A Based on WO 2002036169; EP 1353701 A2 Based on WO 2002036169
PRAI US 2000-244499P 20001031; US 2001-999820 20011031
AB WO 200236169 A UPAB: 20020916
NOVELTY - Pharmaceutical formulation comprising biodegradable polymer in combination with a conjugate of bioactive molecule and a hydrophilic polymer, is new.
DETAILED DESCRIPTION - An INDEPENDENT CLAIM is included for increasing bioavailability or reducing immunogenicity of a bioactive molecule involving conjugating the bioactive molecule with a hydrophilic polymer, formulating the conjugated bioactive molecule with a

biodegradable polymer, and then administering the resulting formulation to a subject.

USE - The formulation is useful for controlled release and systemic delivery of the bioactive molecule to a subject, for increasing bioavailability or for reducing immunogenicity of the bioactive molecule (claimed).

ADVANTAGE - The formulation provides protection from degradation and denaturation under encapsulation in drug carrier. The formulation provides a lower total dose thus benefiting both the patient and producer. Immunogenecity of pegylated bioactive molecules encapsulated in biodegradable polymer drug delivery carriers is decreased relative to non-peglyated bioactive molecules in the carriers. The formulation provides reduced immunogenecity, increased bioavailability, increased duration, increased stability, decreased burst and controlled, sustained release of bioactive molecules in vivo.

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TECH UPTX: 20020916

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Formulation: The bioactive molecule and the hydrophilic polymer are covalently conjugated. The biodegradable polymer is formulated into microparticles or nanoparticles encapsulating the conjugate. The bioactive molecule and the hydrophilic polymer are covalently conjugated.

TECHNOLOGY FOCUS - POLYMERS - Preferred Components: The biodegradable polymer is polyhydroxy acid, **polylactic** acid or **polyglycolic** acid or their copolymers, polyanhydride, polyorthoester or polysaccharide polymer. The hydrophilic polymer is polyethylene glycol, polypropylene glycol or their linear and branched derivatives.

TECHNOLOGY FOCUS - BIOLOGY - Preferred Components: The bioactive molecule is alpha-interferon, beta-interferon, gamma-interferon, erythropoietins, granulocyte colony stimulating factor, granulocyte macrophage colony stimulating factor, interleukin 1, interleukin 2, interleukin 3, interleukin 12, asparaginase, adenosine deaminase, insulin, adrenocorticotropin hormone (ACTH), glucagon, somatostatin, somatotropin, thymosin, parathyroid hormone, pigmentary hormones, somatomedin, leuteinizing hormone, chorionic **gonadotropin**, hypothalmic **releasing factors**, antidiuretic **hormones**, thyroid stimulating hormone, endorphins, enkephalins, biphalin, prolactin, monoclonal antibodies, polyclonal antibodies, antisense oligonucleotides, aptamers, therapeutic genes, heparin, low molecular weight heparin or small bioactive molecules.

L9 ANSWER 3 OF 3 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
AN 2001-257426 [26] WPIDS
DNC C2001-077460
TI Microspheres for continuous release of active agent, particularly leuprolide, in physiological medium, comprises **copolymer** of **glycolic** acid and **lactic** acid, and active agent homogeneously distributed within matrix of **polymer** body.
DC A96 B04 B07
IN MURTAGH, J; THANOO, B C
PA (OAKW-N) OAKWOOD LAB LLC
CYC 93
PI WO 2001010414 A1 20010215 (200126)* EN 25p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC

LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US VN YU ZA ZW

AU 2000065104 A 20010305 (200130)

ADT WO 2001010414 A1 WO 2000-US21038 20000802; AU 2000065104 A AU 2000-65104 20000802

FDT AU 2000065104 A Based on WO 2001010414

PRAI US 1999-366995 19990804

AB WO 200110414 A UPAB: 20010515

NOVELTY - Microspheres (I) for continuous release of an active agent in a physiological medium comprises: (i) **copolymer** of **glycolic** acid and **lactic** acid; and (ii) active agent homogeneously distributed within matrix of **polymer** body, where average number and size of active agent in a particular unit area is the same as a second average number and size of the active in a different unit area of (I).

DETAILED DESCRIPTION - Microspheres (I) for continuous release of effective amounts of an active agent in a physiological medium comprises: (i) a **copolymer** of **glycolic** acid and **lactic** acid;

(ii) an active agent which is homogeneously distributed within a matrix of the polymer body, where an average number and size of the active agent in a particular unit area is substantially the same as a second average number and size of the active in a different unit area of (I). (I) have an average cross-sectional porosity less than 10% of the total cross-sectional area.

INDEPENDENT CLAIMS are also included for the following:

(A) microspheres (I') for continuous release of effective amounts of an active agent in a physiological medium comprising: (a) a homopolymer of lactic acid; and (b) an active agent as in (ii). (I') has an average cross-sectional porosity less than 10% of the total cross-sectional area;

(B) a pharmaceutical composition comprising microspheres for slow continuous release of effective amounts of a water-soluble active agent in an aqueous physiological medium, where the microspheres comprising a poly(lactide-co-glycolide) copolymer. The active agent is a leuprolide drug at 12-20% homogeneously distributed within a matrix of the polymer bodies, where the leuprolide release is predominantly erosion controlled. The erosion control degrades the polymeric leuprolide-containing matrix and releases a continuous effective amount of the leuprolide into the aqueous physiological medium for at least thirty days. Each of the microspheres has a total cross-sectional porosity less than 10% of the total cross-sectional area;

(C) slow release leuprolide microspheres having a cross-sectional porosity of less than 10% prepared by:

(a) forming a dispersed phase comprising a homogeneous solution of a leuprolide drug and a copolymer of lactide and glycolide;

(b) providing a continuous phase in which the dispersed phase will form an emulsion;

(c) continuously introducing dispersed phase into a reactor vessel at dispersed phase feed rate, and continuous phase into the reactor vessel at a continuous phase feed rate, the reactor vessel including means for forming an emulsion, and forming an emulsion of the dispersed phase in the continuous phase;

(d) continuously transporting the emulsion from the reactor vessel to a solvent removal vessel to remove solvent.

USE - As continuous release microspheres for releasing an active agent into a surrounding physiological medium. The active agent includes steroids, diuretics, carbohydrates, amino acids, proteins, enzymes, peptide hormones, analgesic agents, antimalarials, antibiotics, antineoplastics, CNS depressants and stimulants, adrenergic agents, cholinergics, sulfonamides, sulfones, folate reductase inhibitors,

vitamins, diagnostic agents, chelating agents and anti-infective agents. The active agent is especially leuprolide acetate which is an agonist derivative of leutenizing hormone-releasing hormone (LH-RH, i.e. **gonadotropin-releasing hormone**) and which controls and regulates both male and female reproduction. Leuprolide acetate may be used as an antineoplastic agent for treating e.g. endometriosis, anemia secondary to leiomyoma, breast neoplasm, prostate neoplasm, endometrial neoplasm and uterine neoplasm. Leuprolide acetate suppresses testosterone levels and offers an alternative to an orchiectomy (surgical removal of the testicles) or estrogen administration (as testosterone promotes the growth of cancerous cells in the prostate).

ADVANTAGE - The microspheres can be produced using a simple, continuous, economic and efficient process which gives a product of uniform characteristics throughout the production cycle (cf. prior art processes which are unable to produce microspheres having identical characteristics at the end of the production run as ones produced at the beginning and middle of the run). The microspheres have low porosity and are exceptionally uniform in terms of e.g. size and agent load. Due to the low porosity and fine distribution of active agent within the microsphere, the drug release profile during polymer degradation is constant and highly uniform.

5 x 1000 ml Fractions of microsphere suspension produced in a reactor using 8.75 g RG503H (see 'Example'), 1.25 g leuprolide acetate, 45 g CH2Cl2 and 10.7 g MeOH as the dispersed phase, and 5000 ml 0.35% polyvinyl alcohol (PVA) as the continuous phase were collected. The microspheres of each fraction were separated by filtration, freeze dried in bulk and compared. Microscopic analysis showed that the morphology of the microspheres obtained in all five fractions was identical. E.g. Fractions 1-5 had a load (in %) of : 11.17, 11.31, 10.96, 11.05 and 10.99 respectively; bulk density of: 0.40, 0.48, 0.48, 0.47 and 0.48 respectively; and 50% under (in micro m) of: 18.1, 17.4, 17.8, 17.8 and 17.4 respectively. The figures showed that each fraction of microspheres produced throughout the process had excellent consistency.

Dwg.0/0

TECH UPTX: 20010515

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Microspheres: (I) and (I') have an average cross-sectional porosity less than 5% of the total cross-sectional area. (I) have an average particle size of 10-40 microm and an active agent load of at least 9 (preferably at least 15) %. (I') have an average particle size of 10-40 microm, and an active agent load of at least 15%. The continuous release of the active agent within the polymer matrix is essentially by polymer degradation. The active agent is continuously released in an effective amount from (I) over a period of at least 30 days. In (I'), the active agent, leuprolide, is continuously released in an effective amount from each microsphere over a period of at least 90 (preferably 120) days. The active agent is water soluble.

TECHNOLOGY FOCUS - POLYMERS - The poly(lactide-co-glycolide) copolymer has a ratio of glycolide to lactide of 1:1 and an average molecular weight of 26000-36000.

L14 ANSWER 1 OF 25 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
AN 2004-026122 [03] WPIDS
DNC C2004-008640
TI Manufacturing microcapsule of gonadotropic **releasing hormone** enhancement agonist, involves preparing water/oil-type emulsion containing water-soluble medicine, dispersing in outer water

phase and drying.
DC A96 B04 B07
PA (TOYA-N) TOYO YAKUHIN KOGYO KK
CYC 1
PI JP 2003171264 A 20030617 (200403)* 6p
ADT JP 2003171264 A JP 2001-374808 20011207
PRAI JP 2001-374808 20011207
AB JP2003171264 A UPAB: 20040112
NOVELTY - A method for manufacturing microcapsule involves preparing water/oil-type emulsion containing water-soluble medicine as inner water phase and polymeric polymer as oil phase, dispersing water-oil-type medicine in outer water phase to obtain water-oil-water type emulsion and drying to obtain **sustained-release** microcapsule of water-soluble medicine.
DETAILED DESCRIPTION - A method for manufacturing microcapsule involves preparing water/oil-type emulsion containing water-soluble medicine as inner water phase and polymeric polymer as oil phase, dispersing water-oil-type medicine in outer water phase to obtain water-oil-water type emulsion and drying to obtain **sustained-release** microcapsule of water-soluble medicine. A water-soluble metallic salt compound is added to outer water phase at the time of preparing water-oil-type emulsion. INDEPENDENT CLAIMS are also included for the following:
(1) **sustained-release** microcapsule of water-soluble medicine; and
(2) pharmaceutical containing **sustained-release** microcapsule.
USE - For preparing microcapsule of gonadotropic **releasing hormone** enhancement agonist and water-soluble medicine having the same action as that of lutenizing hormone **releasing hormone** or lutenizing hormone **releasing hormone** (claimed).
ADVANTAGE - The method is cost effective and the microcapsule shows excellent **sustained-release** effect.
Dwg.0/0
TECH UPTX: 20040112
TECHNOLOGY FOCUS - INORGANIC CHEMISTRY - Preferred Components: The water-soluble metallic salt is alkaline earth metal or transition metal salt, preferably zinc compound, e.g. zinc acetate, zinc sulfate or zinc chloride. The **polymeric polymer** is **poly lactic** acid or a **copolymer** of **lactic** acid and **glycolic** acid.

L14 ANSWER 2 OF 25 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
AN 2003-778890 [73] WPIDS
DNC C2003-214335
TI Stabilized immunostimulating complex, useful for vaccination, e.g. against human immune deficiency viruses, comprises cationic peptide immunogen and anionic oligonucleotide.
DC A25 A96 B04 D16
IN SOKOLL, K K
PA (SOKO-I) SOKOLL K K; (UNBI-N) UNITED BIOMEDICAL INC
CYC 102
PI WO 2003068169 A2 20030821 (200373)* EN 159p
RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS LU MC MW MZ NL OA PT SD SE SI SK SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SC SD SE SG SK SL TJ TM TN TR TT TZ UA UG UZ VC VN YU ZA ZM

ZW
US 2003165478 A1 20030904 (200373)
ADT WO 2003068169 A2 WO 2003-US4711 20030214; US 2003165478 A1 US 2002-76674 20020214
PRAI US 2003-76674 20030131; US 2002-76674 20020214
AB WO2003068169 A UPAB: 20040115
NOVELTY - Stabilized immunostimulating complex (A) contains a cationic peptide immunogen (I) and an anionic CpG oligonucleotide (ON).

DETAILED DESCRIPTION - Stabilized immunostimulating complex (A) contains a cationic peptide immunogen (I) and an anionic CpG oligonucleotide (ON). (I) has net positive charge at pH 5-8, calculated by assigning +1 to Lys, Arg and His, -1 to Asp and Glu, and 0 to other amino acids, while ON has net negative charge (at same pH) and is a single-stranded DNA of 8-64 nucleotides (nt) with 1-10 repeats of the CpG motif.

INDEPENDENT CLAIMS are also included for the following:
(1) preparation of (A);
(2) preparation of a water-in-oil emulsion of (A);
(3) preparation of a suspension containing (A); and
(4) composition comprising a suspension of (A) in distilled deionized water, saline and phosphate buffered saline.

ACTIVITY - Virucide; Anti-HIV; Cytostatic; Nootropic; Neuroprotective; Antibacterial; Antiallergic; Protozoacide.

MECHANISM OF ACTION - Vaccine; Synergist.

Rats were immunized intramuscularly (3 times at intervals of 4 weeks) with 25 micro g luteinizing hormone **releasing hormone** (LHRH) **peptides** complexed with oligonucleotide (CpG1) at 4:1 charge ratio formulated in aqueous saline containing aluminum hydroxide. The log antibody titer after 12 weeks was about 4; compared to 3 using free peptide and about 3.7 using the complex without adjuvant. Serum testosterone was reduced practically to zero after 6 weeks.

5'-TCGTCGTTTTGTCGTTTTGTCGTTTTGTCGTT (CpG1)

USE - The complex is immunostimulatory (claimed). (A), when formulated in an emulsion, are used as vaccines, especially (claimed) for treatment or prevention of allergy ((I) are derived from immunoglobulin E); HIV infection; androgen/estrogen-dependent tumors ((I) are derived from luteinizing hormone **releasing hormone** (LHRH), also useful for immunological castration and removal of boar taint); foot-and-mouth disease; Alzheimer's disease; bacterial urinary tract infections; malaria and for growth promotion in livestock ((I) are derived from somatostatin).

ADVANTAGE - (A) provide **controlled release** and can be incorporated into vehicles that target specific cell types. (I) and ON show a synergistic increase in the immune response, especially ON upregulates both parenteral and mucosal responses.

Dwg.0/16

TECH UPTX: 20031112

TECHNOLOGY FOCUS - BIOLOGY - Preferred Immunogen:(I) is a synthetic peptide containing a B cell, cytotoxic T cell or helper T cell epitope, particularly with positive charge at least +2. It is derived from HIV CD4; luteinizing hormone **releasing hormone** (LHRH); immunoglobulin E (IgE) or foot-and-mouth disease virus. It is a one of 10 27-65 amino acid sequences as given in the specification.

Preferred Oligonucleotide: ON contains 18-48 bases and 3-8 CpG motifs and is particularly of formula 5'-X1CGX2 or 5'-(X1)2CG(X2)2T. Particularly they are modified by phosphorothioates. It is either a 32 or 24 base length oligomer as given in the specification.

X1 = A, T or G;
X2 = C or T; and
provided that C and G are unmethylated.

Preferred Preparation: (I) is dissolved or dispersed in an aqueous phase, with pH below the ionization point of (I)), and treated dropwise with an aqueous solution of ON to form (A) with (I):(II) charge ratio 1-16:1, particularly 16, 4, 2, 1.5 or 1:1. Both (I) and ON are formulated in distilled deionized water, saline and/or phosphate-buffered saline. The complex may then be recovered by lyophilization or spray-drying and has average particle size 1-50 (preferably 1-15) microm.
Preferred Emulsion: To prepare a water-in-oil emulsion, (A), prepared in aqueous phase, is added to a continuous phase of synthetic, vegetable, mineral and/or metabolizable animal oil and dispersed under mechanical shear. Preferably two syringes are filled, one with the aqueous phase and the other with oil (intrinsic viscosity below 1500 mPa), connected through narrow bore tubing to a housing that supports a membrane of controlled size (0.05-20 microm). The aqueous phase is extruded into the oil phase by repeated exchange through the membrane. The aqueous phase may also contain a surfactant and/or emulsion stabilizer (particularly a mannide-oleate or its derivative), optionally also an adjuvant (Ad1). The oil phase may also include an adjuvant (Ad2). Alternatively, dry (A) is reconstituted in an in situ gelled polymer (X), formed in a biocompatible solvent (specifically dimethyl sulfoxide, N-methylpyrrolidone, triacetin or glycerol) at concentration 5-50wt.%, optionally in presence of Ad1.
Preferred Suspension: To produce a suspension, (A), in aqueous phase, is added to an aqueous suspension of an inorganic salt (Y), with mixing. Alternatively, an aqueous solution of (I) is added to the (Y), then ON added. The aqueous phase may include a surfactant; tonifier (e.g. phosphate-buffered saline) and/or preservative (especially 2-phenoxyethanol or its derivative).
Preferred Adjuvants: The composition further comprises Ad1. Ad1 is MPL (RTM; monophosphonyl lipid A), muramyl dipeptide (MDP), dimethyl dioctadecyl ammonium bromide (DDA), aviridine, BAY-1005, DC-Chol, murapalmitine, poly(di(carboxylatophenoxy)) phosphazene, a saponin, a cholera toxin, a heat labile Enterotoxin from Escherishia coli and interleukins 1beta, 2 or 12, and interferon-gamma.

TECHNOLOGY FOCUS - **POLYMERS** - (X) is a poly(D,L-lactide-co-glycolide) or **poly**(D,L-**lactic** acid-co-**glycolic** acid) **copolymer**; polycaprolactone; polyanhydride; poly(ortho-ester) or poly(alpha-hydroxybutyric acid). Most preferred are **copolymers** of formula R1-(CO-CHMe-O-)x(CO-CH2O)y-H
R1 = hydroxy or 1-5C alkoxy;
x:y = ratio of monomer units
They have molecular weight 2-100 kD and inherent viscosity 0.1-1 dl/g.

TECHNOLOGY FOCUS - INORGANIC CHEMISTRY - (Y) are aluminum hydroxide; aluminum phosphate and calcium phosphate.

L14 ANSWER 3 OF 25 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
AN 2003-247906 [24] WPIDS
DNC C2003-063771
TI **Sustained-release** composition useful for preventing or treating e.g. prostate cancer comprises a **lactic** acid-**glycolic** acid **polymer** having specific weight ratio and active substance.
DC A96 B07
IN HATA, Y; YAMADA, A; YAMAMOTO, K
PA (TAKE) TAKEDA CHEM IND LTD
CYC 99
PI WO 2003002091 A2 20030109 (200324)* EN 30p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZM ZW

W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK
DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KR KZ
LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO
RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VN YU ZA ZM ZW

JP 2003206243 A 20030722 (200351) 13p

ADT WO 2003002091 A2 WO 2002-JP6526 20020628; JP 2003206243 A JP 2002-189244 20020628

PRAI JP 2001-340980 20011106; JP 2001-199462 20010629

AB WO2003002091 A UPAB: 20030410

NOVELTY - **Sustained-release** composition (C1) comprises a **lactic** acid-**glycolic** acid **polymer** (a) having a ratio of weight average molecular weight to number average molecular weight of 1.90 or lower or its salt and an active substance (b).

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are included for the following:

(1) preparation of (C1) involving removing a solvent from a mixed solution containing (b) or its salt and (a);

(2) preparation of (a) (having a average molecular weight of 8000 - 15000 and having a ratio of weight average molecular weight to number average molecular weight of at most 1.90) or its salt involving adding water to an organic solvent containing (a), having average molecular weight of about 5000 - 15000 at a ratio of less than 5 - 50 (ratio by volume), relative to 100 of the organic solvent; and

(3) microsphere (preferably microcapsule) containing (a) (having weight average molecular weight of 11600 - 14000) or its salt and a luteinizing hormone-**releasing hormone** (LH-RH) derivative or its salt. The microsphere is free of gelatin.

ACTIVITY - Gynecological; Cytostatic; Neuroprotective; Nootropic; Immunosuppressive; Antitumor.

MECHANISM OF ACTION - None given.

USE - For preventing or treating prostate cancer, prostatomegaly, endometriosis, hysteromyoma, metrofibroma, precocious puberty, and dysmenorrhea or as contraceptive; for preventing breast cancer after the operation for premenopausal breast cancer (all claimed). Also useful as an agent for preventing and treating hormone dependent diseases e.g. sex hormone dependent cancers (e.g. uterine cancer and pituitary gland tumor), amenorrhea, multiocular ovary syndrome, Alzheimer's disease, autoimmune diseases, benign or malignant tumors (sensitive to LH-RH).

ADVANTAGE - The composition releases (b) (preferably LH-RH derivative) over at least two weeks. The composition is free of a drug retaining substance (e.g. gelatin) and contains (b) in a large amount thus achieving a stable release rate over about 1 month by suppressing any initial excessive release of (b). The composition has low toxicity and can be used as a safe medicine.

Dwg.0/0

TECH UPTX: 20030410

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Active Agent:(b) is a LH-RH derivative. (b) is slightly water-soluble or water-soluble. The LH-RH derivative (5 - 24 w/w.%)), is a peptide of formula 5-oxo-Pro-His-Trp-Ser-Tyr-Y-Leu-Arg-Pro-Z or its salt (preferably 5-oxo-Pro-His-Trp-Ser-Tyr-Dleu-Leu-Arg-Pro-C2H5 (leuprorelin) or its acetate).

Y = DLeu, DAla, DTrp, Dser(tBu), D2Nal or DHis(ImBzl); and

Z = HN, C2H5 or Gly-NH2.

TECHNOLOGY FOCUS - **POLYMERS** - Preferred Components: (a) has a weight average molecular weight of 3000 - 100000 (preferably 8000 - 15000). (a) (having molecular weight of at most 3000), has the ratio of the low molecular weight fraction of at most 9 (preferably 3 - 9%). The **polymer** has a molar ratio of **lactic** acid to **glycolic** acid of 100:0 - 40:60 (preferably 70:30 - 80:20).

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preferred Method: The method of preparing (C1) involves mixing and dispersing (b) or its salt in an organic solvent solution containing (a) and removing the organic solvent. (b) is used as an aqueous solution.
Preferred Components: The organic solvent is hydrophilic (preferably acetone). The ratio of water relative to 100 of the organic solvent is 10 - 45 (preferably 40) (ratio by volume).

L14 ANSWER 4 OF 25 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
AN 2002-730928 [79] WPIDS
CR 2000-052778 [04]; 2003-898494 [82]
DNN N2002-576148 DNC C2002-207013
TI Stabilized formulation containing crystals of protein or nucleic acid, useful e.g. for slow release of therapeutic agents or vaccinating antigens.
DC A96 B04 C06 D16 D21 D22 P32
IN KHALAF, N K; MARGOLIN, A L; RAKESTRAW, S L; SHENOY, B C; ST CLAIR, N L
PA (KHAL-I) KHALAF N K; (MARG-I) MARGOLIN A L; (RAKE-I) RAKESTRAW S L; (SHEN-I) SHENOY B C; (SCLA-I) ST CLAIR N L; (ALTU-N) ALTUS BIOLOGICS INC
CYC 1
PI US 2002045582 A1 20020418 (200279)* 65p
US 6541606 B2 20030401 (200324)
ADT US 2002045582 A1 Provisional US 1997-70274P 19971231, Provisional US 1998-83148P 19980427, CIP of US 1998-224475 19981231, Cont of WO 1999-US9099 19990427, US 1999-374132 19990810; US 6541606 B2 Provisional US 1997-70274P 19971231, Provisional US 1998-83148P 19980427, CIP of US 1998-224475 19981231, Cont of WO 1999-US9099 19990427, US 1999-374132 19990810
PRAI US 1999-374132 19990810; US 1997-70274P 19971231; US 1998-83148P 19980427; US 1998-224475 19981231; WO 1999-US9099 19990427
AB US2002045582 A UPAB: 20031223
NOVELTY - Formulation (A) comprises a protein crystal (PC) and at least one stabilizing ingredient (I) with at least 60% greater shelf life at 50 deg. C than a PC without (I), is new.
DETAILED DESCRIPTION - Formulation (A) comprises a protein crystal (PC) and at least one stabilizing ingredient (I) with:
(i) at least 60-fold greater shelf life (measured as half-life) at 50 deg. C than the soluble protein, in solution;
(ii) at least 59-fold greater shelf life at 40 deg. C and 75% humidity than PC without (I);
(iii) at least 60% greater shelf life at 50 deg. C than PC without (I);
(iv) less than 20% loss of alpha -helical content (measured by Fourier-transform infra-red spectroscopy) after 4 days storage at 50 deg. C whereas the soluble protein loses more than 50% after 6 hr; or
(v) a combination of (i) and (iv).
INDEPENDENT CLAIMS are also included for the following:
(1) formulation (A1) comprising PC in which the protein is larger than 10 kD and at least one ingredient (Ia);
(2) formulation (A2) comprising a nucleic acid crystal (NAC) and at least one (Ia);
(3) composition for release of protein comprising a PC, optionally also (Ia), embedded in a matrix of polymeric carrier;
(4) composition for release of nucleic acid comprising (A2) encapsulated within a matrix of polymeric carrier;
(5) PC composition (B) comprising PC embedded in a matrix of polymeric carrier;
(6) method (M1) for producing microspheres (MC) by encapsulating PC, while maintaining their crystallinity;

(7) protein delivery system comprising (B);
(8) method (M2) for producing, dried, non-crosslinked PC or NAC ; and
(9) dried, non-crosslinked PC or NAC.
ACTIVITY - None given.
MECHANISM OF ACTION - Vaccine.
No supporting data is given.
USE - (A), and similar formulations containing nucleic acid crystals (NAC) instead of PC, are pharmaceutical, food, feed, veterinary, diagnostic, cosmetic, personal care or decontaminating formulations, especially for therapeutic (**sustained**) **release** of proteins or nucleic acid, e.g. enzymes or vaccinating antigens.
ADVANTAGE - In the new formulations, proteins, and nucleic acids, that are unstable in solution can be stored, dry, for long periods and can be reconstituted to provide highly concentrated parenteral formulations, particularly for subcutaneous delivery. The size and shape of the crystals can be **controlled** to alter the **release** rate.
Dwg.9/24

TECH UPTX: 20021209
TECHNOLOGY FOCUS - BIOLOGY - Preferred Proteins: In (A), these include (i) enzymes, especially lipase, glucose oxidase and penicillin acylase; (ii) therapeutic proteins, e.g. antibodies, human serum albumin, human growth hormones, nerve growth hormones, bone morphogenic hormones, fertility hormones, leukocyte markers, histocompatibility antigens, mucins, integrins, adhesion molecules, selectins, interleukins, interleukin receptors, chemokines, growth factors, growth factor receptors, interferon receptors, immunoglobulins, T-cell receptors, blood factors, leukocyte markers, CD2, CD3, CD4, CD5, CD6, CD7, CD8, CD11a, CD11b, CD11c, CD13, CD14, CD18, CD19, CE20, CD22, CD23, CD27, CD28, B7.1, B7.2, B7.3, CD29, CD30, CD40, gp39, CD44, CD45, Cdw52, CD56, CD58, CD69, CD72, CTLA-4, LFA-1, TCR, histocompatibility antigens, MHC class I, MHC class II, SLex, SLey, SLea, SLeb, VLA-1, VLA-2, VLA-3, VLA-4, VLA-5, VLA-6, LFA-1, Mac-1, p150, p95, L-selectin, P-selectin, E-selectin, VCAM-1, ICAM-1, ICAM-2, LFA-3, IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-11, IL-12, IL-13, IL-14, IL-15, IL-1R, IL-2R, IL-4R, IL-5R, IL-6R, IL-7R, IL-8R, IL-10R, IL-11R, IL-12R, IL-13R, IL-14R, IL-15R, PF4, RANTES, MIP1α, MCP1, NAP-2, Groα, Groβ, and IL-8, TNFalpha, TGFbeta, TSH, VEGF/VPF, PTHrP, EGF family, EGF, PDGF family, endothelin, gastrin **releasing peptide** (GRP), TNFalphaR, RGFbetaR, TSHR, VEGFR/VPFR, FGFR, EGFR, PTHrPR, PDGFR family, EPO-R, GCSF-R, IFNαR, IFNβR, IFNγR, IgE, FceRI, FceRII, complement C3b, complement C5a, complement C5b-9, Rh factor, fibrinogen, fibrin and myelin associated growth inhibitor. Also vaccine antigens selected from the group consisting of viral surface proteins, HIV-1 envelope glycoproteins, RSV envelope glycoproteins, HSV envelope glycoproteins, EBV envelope glycoproteins, VZV envelope glycoproteins, HPV envelope glycoproteins, Influenza virus glycoproteins, Hepatitis family surface antigens; viral structural proteins, viral enzymes, parasite proteins, parasite glycoproteins, parasite enzymes, bacterial proteins, tumor antigens, allergens and toxins.
In (B), suitable proteins are glyco-, sulfo-, iodo-, or methyl-substituted proteins; fusion proteins; enzymes; hormones; antibodies and cytokine peptides.
Preferred Materials: The ingredient is an excipient, e.g. sucrose, trehalose, hydroxy-beta-cyclodextrin or a polymer. The preferred non-synthetic polymeric carrier is albumin, but also suitable are e.g. cellulose or its derivatives, gelatin, sulfated polysaccharides etc.
Preferred Crystals: In (B), PC have largest diameter 0.01-500, especially 50-100, micron; especially they are microcrystals, optionally crosslinked with a multi- (especially bi-) functional crosslinking agent (II).
Preferred Processes: In (M1), PC are suspended in a solution of polymeric

carrier in organic solvent (especially dichloromethane) to form a suspension of coated crystals. This suspension is added to an aqueous solution containing an emulsifier, then the carrier hardened by evaporating solvent in presence of emulsifier. In (M2), protein or nucleic acid is converted to crystals, these washed with organic solvent or liquid polymer, then solvent removed and the crystals dried. The crystals may then be dissolved in appropriate buffer and formulated with pharmaceutical ingredients.

TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preferred Nucleic Acid: This is DNA or RNA, especially encoding (or comprising) a ribozyme or encoding any of the proteins specified above.

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preferred Materials: Specified (II) are glutaraldehyde, succinaldehyde, octanedialdehyde or glyoxal. Suitable solvents in (M2) include acetone, methanol, ethyl acetate and many others.

TECHNOLOGY FOCUS - **POLYMERS** - Preferred **Polymers**: Specified **polymeric** excipients are (methoxy)poly(ethylene glycol). **Polymeric** carriers are biodegradable or biocompatible selected from one or more of the group consisting of poly (acrylic acid), poly (cyanoacrylates), poly (amino acids), poly (anhydrides), poly (depsipeptide), **poly** (esters), **poly** (**lactic** acid), **poly** (**lactic**-co-**glycolic** acid) or PLGA, **poly** (β-hydroxybutryate), poly (caprolactone), poly (dioxanone); poly (eth ylene glycol), poly ((hydroxypropyl) methacrylamide, poly ((organo)phosphazene), poly (ortho esters), poly (vinyl alcohol), poly (vinylpyrrolidone), maleic anhydride-alkyl vinyl ether **copolymers**, pluronic polyols, albumin, alginate, cellulose and cellulose derivatives, collagen, fibrin, gelatin, hyaluronic acid, oligosaccharides, glycaminoglycans, sulfated polysaccharides, blends and **copolymers**. Most preferred are **poly**(**lactic**-co-**glycolic** acid) and albumin. The **polymeric** carrier is emulsified with poly(vinyl alcohol).

L14 ANSWER 5 OF 25 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
AN 2002-519085 [55] WPIDS
DNC C2002-146757
TI Thermogelling biodegradable aqueous polymer solution, for use in a bioactive agent delivery system, comprises a biodegradable polymer consisting of polyethylene glycol and biodegradable polyester blocks, and an aqueous solution.
DC A23 A25 A96 B05 B07
IN GUTOWSKA, A; JEONG, B M
PA (BATT) BATTELLE MEMORIAL INST; (GUTO-I) GUTOWSKA A; (JEON-I) JEONG B M
CYC 96
PI WO 2002026215 A2 20020404 (200255)* EN 37p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW
AU 2001094828 A 20020408 (200255)
US 2002173586 A1 20021121 (200279)
ADT WO 2002026215 A2 WO 2001-US30322 20010927; AU 2001094828 A AU 2001-94828 20010927; US 2002173586 A1 Provisional US 2000-236926P 20000928, US 2001-833460 20010411
FDT AU 2001094828 A Based on WO 2002026215
PRAI US 2001-833460 20010411; US 2000-236926P 20000928

AB WO 200226215 A UPAB: 20020829
NOVELTY - A thermogelling biodegradable aqueous polymer solution comprising:
(a) a biodegradable polymer consisting of:
(i) a polyethylene glycol (PEG) block; and
(ii) a biodegradable polyester block; and
(b) an aqueous solution, is new.
DETAILED DESCRIPTION - A new thermogelling biodegradable aqueous polymer solution comprises:
(a) a biodegradable polymer consisting of:
(i) a polyethylene glycol (PEG) block; and
(ii) a biodegradable polyester block, wherein the blocks are linked to form a polymer of formula (I); and
(b) an aqueous solution.
An(B) (I)
n = greater than 2, (preferably 3 - 10); and
A and B = different from each other and selected from a polyethylene glycol block and biodegradable polyester block.
INDEPENDENT CLAIMS are also included for the following:
(1) a biodegradable bioactive agent delivery system comprising a bioactive agent contained in the new thermogelling biodegradable aqueous polymer solution;
(2) parenteral delivery of a bioactive agent in a thermogelling polymer matrix to a warm blooded animal for the **controlled release** of the bioactive agent comprising:
(i) mixing the new thermogelling biodegradable aqueous polymer solution with a bioagent to form a polymer-bioactive agent mixture;
(ii) maintaining the mixture at a temperature below the gelling temperature of the polymer; and
(iii) injecting the solution parenterally into the warm blooded animal, forming a gel depot of the bioactive agent and biodegradable polymer as the temperature of the solution is raised by the body temperature of the animal to be above the gelling temperature of the polymer; and
(3) the biodegradable polymer (a).
ACTIVITY - Cytostatic; hormonal; antibacterial; analgesic; antiinflammatory; antidepressant; anticonvulsant; antimalarial; immunostimulant; antiarthritic. No biological data is given.
MECHANISM OF ACTION - Narcotic antagonist; vaccine; gene therapy; antisense gene therapy; peptide therapy.
USE - The polymer solution is used for providing in situ forming, biodegradable implants. They are also used as a bioactive agent (i.e. drug) delivery system. The system is very good for the local delivery of bioactive agents such as proteins, anticancer drugs and anti-arthritis drugs.
ADVANTAGE - Delivery systems comprising the new polymer solution allow control of the stability of drugs and drugs dosage from one day to two months. The systems are biodegradable and demonstrate desirable release rates. Thermosensitivity enables the in situ gel formation on injection, therefore no surgical procedure is required to implant the drug delivery system and no organic solvent is needed for drug formulation. The physical properties of the soft hydrogels reduce mechanical tissue irritation surrounding the injection site. The polymers are biodegradable, which means the implants do not need to be removed by surgery after release of the pharmaceutical agent.
Dwg.0/13

TECH UPTX: 20020829
TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Bioactive Agent: The bioactive agent is a drug that is selected from anti-cancer agents (most preferred), hormones, antibiotics, narcotic antagonists, analgesics,

antiinflammatory agents, antidepressants, anti-epileptics, antimalarial agents, immunoactivators, growth factors, radioprotection agents, vaccines, gene therapy agents, oligonucleotides, antisense, peptides (preferred) and /or proteins. The preferred anti-cancer agent is selected from adriamycin, mitomycin, bleomycin, cisplatin, carboplatin, doxorubicin, daunorubicin, 5-fluoroacil, methotrexate, taxol, taxotere and actinomycin D. The preferred polypeptide is selected from oxytocin, vasopressin, adrenocorticotropic growth factor (PDGF), prolactin, luliberin or luteinising hormone **releasing hormone** (LHRH), growth hormone, growth hormone **releasing factor** , insulin, somatostatin, glucagons, interleukin-2 (IL-2), interferon-alpha,beta,eta (IFN- alpha,beta,eta), gastrin, tetragastrin, pentagastrin, urogastroine, secretin, cacitonin, enkephalins, endorphins, angiotensins, thyrotropin **releasing hormone** (TRH), tumor necrosis factor (TNF), nerve growth factor (NGF), granulocyte-colony stimulating factor (G-CSF), granulocyte macrophage-colony stimulating factor (M-CSF), rennin, bradyldnin, bacitracins, alpha-1 antitrypsin, platelet derived growth factor, albumin, anti-thrombin III, glucocerebrosidase, DNAse, tissue plasminogen activator, calcitonin, clotting factors VII, VIII, and IX, LHRH antagonists, insulin, erythropoietin, polymixins, colistins, tyrocidin, grainicidines, and synthetic analogs, modifications and pharmacologically active fragments of them, monoclonal antibodies and soluble vaccines.

TECHNOLOGY FOCUS - **POLYMERS** - Preferred **Polymer**: The PEG block has an average molecular weight of 300 - 20000, (preferably 500 - 10000). The polyester block has an average molecular weight of 1000 - 30000, (preferably 1000 - 10000), and is selected from **poly**(DL-**lactic** acid), **poly**(L-**lactic** acid), **poly**(**glycolic** acid), **poly**(eta-caprolactone), poly(gamma-butyrolactone), poly(gamma-valerolactone), poly(beta-hydroxybutyric acid) and their **copolymers** or **terpolymers** . More preferably, the **copolymers** or **terpolymers** are selected from **poly**(LD-**lactic**-acid-co-**glycolic** acid), **poly**(L-**lactic**-acid-co-**glycolic** acid), **poly**(eta-caprolactone-co-DL-**lactic** acid) and copoly(eta-caprolactone-co-DL-**lactic** acid-**glycolic** acid).

L14 ANSWER 6 OF 25 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
AN 2002-195592 [25] WPIDS
DNC C2002-060387
TI **Sustained release** compositions comprise nonpeptidyl physiological substance and biodegradable polymer having terminal carboxyl groups.
DC A96 B02 B04 B07
IN HATA, Y; IGARI, Y; YAMAGATA, Y
PA (TAKE) TAKEDA CHEM IND LTD; (HATA-I) HATA Y; (IGAR-I) IGARI Y; (YAMA-I) YAMAGATA Y
CYC 96
PI WO 2001095940 A1 20011220 (200225)* JA 64p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
AU 2001064264 A 20011224 (200227)
JP 2002068982 A 20020308 (200233) 25p
EP 1291023 A1 20030312 (200320) EN

R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR
US 2004023987 A1 20040205 (200411)
ADT WO 2001095940 A1 WO 2001-JP5009 20010613; AU 2001064264 A AU 2001-64264 20010613; JP 2002068982 A JP 2001-180061 20010614; EP 1291023 A1 EP 2001-938630 20010613, WO 2001-JP5009 20010613; US 2004023987 A1 WO 2001-JP5009 20010613, US 2002-297695 20021206
FDT AU 2001064264 A Based on WO 2001095940; EP 1291023 A1 Based on WO 2001095940
PRAI JP 2000-178534 20000614
AB WO 200195940 A UPAB: 20020418
NOVELTY - Composition comprises a nonpeptidyl physiological substance and a biodegradable polymer having at least 2 terminal carboxyl groups or its salt.
ACTIVITY - None given.
MECHANISM OF ACTION - Gonadoliberin Agonist; Gonadoliberin Antagonist
USE - As **sustained release** compositions for administering non-peptidyl physiological substances especially gonadotrophin stimulating hormone **releasing hormone** agonists or antagonists.
ADVANTAGE - Content of active agent can be increased and its release can be regulated or accelerated to achieve required pharmacological effect. Composition has reduced subcutaneous irritation and high stability.
Dwg.0/0
TECH UPTX: 20020418
TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preferred Composition: Composition is formulated for injection or as microcapsules and comprises a gonadotrophin stimulating hormone **releasing hormone** agonist or antagonist having a molecular weight of 1000 or less (preferably a thienopyrimidinedione compound of formula (I) or a thienopyridone compound of formula (II) or their salts) and a **polymer** having alpha,alpha-dicarboxyl groups or alpha,beta,beta'-tricarboxyl groups (preferably a **lactic** acid-**glycolic** acid **copolymer** having omega-tartronic or citric acid groups). Glass transition temperature of the peptide is at least 10 degrees C higher than that of the active compound.
R1, R2 = H, OH, 1-4C alkoxycarbonyl or optionally substituted 1-4C alkyl;
R3 = H, halo, OH or optionally substituted 1-4C alkoxy; or
R3+R3 = 1-4C alkylenedioxy;
R4 = H or 1-4C alkyl;
R6 = benzyl (2-substituted by R5) or optionally substituted 1-4C alkyl;
R5 = H; or
R4+R5 = heterocyclyl;
n = 0-5;
R9 = optionally substituted 1-7C alkyl, 3-7C cycloalkyl, 1-6C alkoxyamino or hydroxylamino; and
R10 = optionally substituted 1-7C alkyl or phenyl;
provided that when R9 = non-substituted alkyl then R10 is substituted alkyl or phenyl.

L14 ANSWER 7 OF 25 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
AN 2002-034220 [04] WPIDS
DNC C2002-009505
TI Drug delivery system for **controlled** protein **release** in warm-blooded animal comprises a protein- or peptide-deposited sparingly soluble biocompatible particle and a biocompatible polymeric matrix.
DC A96 B05 B07
IN PIAO, A; SHIH, C; ZENTNER, G
PA (MACR-N) MACROMED INC

CYC 96
PI WO 2001076558 A1 20011018 (200204)* EN 27p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW
AU 2001051389 A 20011023 (200213)
US 2002015737 A1 20020207 (200213)
EP 1267838 A1 20030102 (200310) EN
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR
KR 2003009425 A 20030129 (200336)
CN 1430504 A 20030716 (200363)
BR 2001010319 A 20030729 (200365)
NZ 521994 A 20030829 (200365)
ADT WO 2001076558 A1 WO 2001-US11217 20010406; AU 2001051389 A AU 2001-51389 20010406; US 2002015737 A1 Provisional US 2000-195700P 20000407, US 2001-827100 20010405; EP 1267838 A1 EP 2001-924765 20010406, WO 2001-US11217 20010406; KR 2003009425 A KR 2002-713405 20021007; CN 1430504 A CN 2001-809982 20010406; BR 2001010319 A BR 2001-10319 20010406, WO 2001-US11217 20010406; NZ 521994 A NZ 2001-521994 20010406, WO 2001-US11217 20010406
FDT AU 2001051389 A Based on WO 2001076558; EP 1267838 A1 Based on WO 2001076558; BR 2001010319 A Based on WO 2001076558; NZ 521994 A Based on WO 2001076558
PRAI US 2001-827100 20010405; US 2000-195700P 20000407
AB WO 200176558 A UPAB: 20020117
NOVELTY - A drug delivery system comprises: a sparingly soluble biocompatible particle; a protein or peptide deposited onto the particle forming an insoluble protein/particle combination; and a biocompatible polymeric matrix having the protein/particle combination dispersed in the matrix.

USE - For **controlled** protein **release** into a biological environment particularly in warm-blooded animals (claimed).

ADVANTAGE - The drug delivery system suppresses the water solubility of the protein or peptide so that the proteins or peptides can be incorporated into long-acting formulations. A single administration may results in long-term release. The composition lowers or eliminates the initial bursts, thus high initial peaks and other fluctuations of protein release are reduced. The proteins or peptides deposited onto these water insoluble particles can also enable the proteins to be stored and processed as dry powders. The rate of drug **release** from the system can be **controlled** by selecting appropriate particles, amount of drug deposited, drug loading parameters, polymeric matrixes, particles, etc.

Dwg.0/5

TECH UPTX: 20020117
TECHNOLOGY FOCUS - INORGANIC CHEMISTRY - Preferred Components: The sparingly soluble biocompatible particle is zinc salt, zinc oxide, magnesium salt, magnesium oxide, calcium salt, and/or calcium oxide (preferably zinc carbonate, zinc oxide, zinc tartrate, zinc hydroxide, zinc phosphate, zinc citrate, magnesium oxide, magnesium hydroxide, magnesium carbonate, calcium oxide, calcium phosphate, calcium sulfate and/or calcium carbonate).
TECHNOLOGY FOCUS - BIOLOGY - Preferred Combination: The protein/particle combination has a biocompatible particle to protein or peptide ratio of 1:10 - 100000:1 (preferably 1:10 - 1000:1) by weight and the combination is present in relation to polymeric matrix at about 0.01 - 30 wt.%.

Preferred Component: The protein or peptide is oxytocin, vasopressin, adrenocorticotropic hormone, epidermal growth factor, platelet-derived growth factor (PDGF), prolactin, luteinizing hormone **releasing hormone** (LHRH), LHRH agonist, growth hormone, growth hormone **releasing factor**, insulin, erythropoietin, somatostatin, glucagon, interleukin (including IL-2, IL-1, IL-12, etc), interferon-alpha, interferon-beta, interferon-gamma, gastrin, tetragastrin, pentagastrin, urogastrone, secretin, calcitonin, enkephalins, endorphins, angiotensins, thyrotropin **releasing hormone** (TRH), tumor necrosis factor (TNF), parathyroid hormone (PTH), nerve growth factor (NGF), granulocyte-colony stimulating factor (G-CSF), granulocyte macrophage-colony stimulating factor (GM-CSF), macrophage-colony stimulating factor (M-CSF), heparinase, vascular endothelial growth factor (VEG-F), bone morphogenic protein (BMP), hANP, glucagon-like peptide (GLP-1), rennin, bradykinin, bacitracins, polymyxins, colistins, tyrocidine, gramicidins, cyclosporins, enzymes, cytokines, enzymes, cytokines, antibodies, vaccines, antibiotics, antibodies and/or glycoprotein (preferably human growth hormone or insulin).

TECHNOLOGY FOCUS - **POLYMERS** - Preferred Matrix: The biocompatible **polymeric** matrix comprises a **polymer** or get material selected from nondegradable **polymers**, biodegradable **polymers**, absorbable **polymers**, bioerodible **polymers** and/or block **copolymers** (preferably biodegradable **polymer**, block **copolymer** or non-degradable **polymer**). The biocompatible **polymeric** matrix is selected from **polymeric** particles, implants, microcapsules, microspheres, nanospheres, **polymeric** gels and/or environment responsive **polymers** or gels.
Preferred Components: The biodegradable **polymer** is poly(lactide), poly(glycolide), poly(lactide-co-glycolide), **poly**(**lactic** acid), **poly**(glycotic acid), **poly**(**lactic** acid-co-**glycolic** acid), polyanhydride, **poly**(ortho ester), poly(eta-carprolactone), poly(hydroxybutyric acid), polyamino acid or its blends or **copolymer.** The block **copolymer** is A-B-A block **copolymer**, B-A-B block **copolymer** and/or A-B block **copolymer.** The A block is a biodegradable **polymer** selected from the biodegradable **polymer** and B block is polyethylene glycol. The nondegradable **polymer** is polyacrylate, polyacrylate ester, silicone rubber, poloxamer, tetronic, polystyrene, poly(methyl methacrylate), polymethyl methacrylate ester, polystyrene, ethylene-vinyl acetate **copolymer**, polyethylene-maleic anhydride **copolymer**, polyamide, **polymer** of ethylene-vinyl acetate, acyl substituted cellulose acetate, nondegradable polyurethane, poly(vinyl chloride), poly(vinyl fluoride), poly(vinyl imidazole, chlorosulfonate polyolefin, poly(ethylene oxide) or its blend or **copolymer.**

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred System: The drug delivery system further comprises a second protein or peptide. The first protein or peptide is deposited onto a surface of the particle and the second protein or peptide is either deposited on the particle dispersed within the polymeric matrix or dispersed within the polymeric matrix. The system has several first and second protein or peptide molecules. A first portion of the protein or peptide molecules are deposited on the particle as part of a protein-particle combination dispersed within the polymeric matrix, and a second portion of the protein or peptide molecules are dispersed within the polymeric matrix.

L14 ANSWER 8 OF 25 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
AN 2001-168445 [17] WPIDS
DNC C2001-050282
TI **Sustained release** composition e.g. for peptides comprises active substance, hydroxynaphthoic acid and **lactic** acid-**glycolic** acid **polymer.**
DC A96 B07
IN HATA, Y; IGARI, Y; YAMAMOTO, K
PA (TAKE) TAKEDA CHEM IND LTD
CYC 94
PI WO 2001005380 A1 20010125 (200117)* JA 49p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TZ UG ZW
W: AE AG AL AM AU AZ BA BB BG BR BY BZ CA CN CR CU CZ DM DZ EE GD GE HR HU ID IL IN IS JP KG KR KZ LC LK LR LT LV MA MD MG MK MN MX MZ NO NZ PL RO RU SG SI SK TJ TM TR TT UA US UZ VN YU ZA
JP 2001081043 A 20010327 (200122) 18p
AU 2000058530 A 20010205 (200128)
CZ 2002000114 A3 20020417 (200231)
NO 2002000084 A 20020314 (200232)
EP 1197208 A1 20020417 (200233) EN
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI
BR 2000012400 A 20020521 (200238)
SK 2002000034 A3 20020509 (200239)
KR 2002012312 A 20020215 (200257)
CN 1361685 A 20020731 (200279)
JP 2001510437 X 20030204 (200320)
HU 2002002880 A2 20030128 (200323)
NZ 516466 A 20030228 (200323)
ZA 2002000347 A 20030326 (200327) 76p
MX 2002000461 A1 20020801 (200367)
ADT WO 2001005380 A1 WO 2000-JP4683 20000713; JP 2001081043 A JP 2000-217251 20000713; AU 2000058530 A AU 2000-58530 20000713; CZ 2002000114 A3 WO 2000-JP4683 20000713, CZ 2002-114 20000713; NO 2002000084 A WO 2000-JP4683 20000713, NO 2002-84 20020108; EP 1197208 A1 EP 2000-944418 20000713, WO 2000-JP4683 20000713; BR 2000012400 A BR 2000-12400 20000713, WO 2000-JP4683 20000713; SK 2002000034 A3 WO 2000-JP4683 20000713, SK 2002-34 20000713; KR 2002012312 A KR 2002-700546 20020114; CN 1361685 A CN 2000-810405 20000713; JP 2001510437 X WO 2000-JP4683 20000713, JP 2001-510437 20000713; HU 2002002880 A2 WO 2000-JP4683 20000713, HU 2002-2880 20000713; NZ 516466 A NZ 2000-516466 20000713, WO 2000-JP4683 20000713; ZA 2002000347 A ZA 2002-347 20020115; MX 2002000461 A1 WO 2000-JP4683 20000713, MX 2002-461 20020114
FDT AU 2000058530 A Based on WO 2001005380; CZ 2002000114 A3 Based on WO 2001005380; EP 1197208 A1 Based on WO 2001005380; BR 2000012400 A Based on WO 2001005380; SK 2002000034 A3 Based on WO 2001005380; JP 2001510437 X Based on WO 2001005380; HU 2002002880 A2 Based on WO 2001005380; NZ 516466 A Based on WO 2001005380; MX 2002000461 A1 Based on WO 2001005380
PRAI JP 1999-201887 19990715
AB WO 200105380 A UPAB: 20010328
NOVELTY - **Sustained release** composition comprises:
(a) physiologically active substance;
(b) hydroxynaphthoic acid; and
(c) a **lactic** acid-**glycolic** acid **polymer**

DETAILED DESCRIPTION - **Sustained release** composition comprises:
(a) physiologically active substance or its salt;
(b) hydroxynaphthoic acid or its salt; and

(c) a **lactic** acid-**glycolic** acid **polymer**
or its salt having a weight-average molecular weight by the amount (micro mol) of the terminal carboxyl group per unit mass (g) of the **lactic** acid-**glycolic** acid **polymer** of 1200000-3000000.

ACTIVITY - Cytostatic;

USE - As a **sustained release** composition especially an injection for peptides such as luteinizing hormone **releasing hormone** (LH-RH) compounds for treating and preventing e.g. prostate cancer, prostatic hypertrophy, uterine cancer, myometrium cancer, pubescent disturbances, uterine fibrosarcoma, and breast cancer.

ADVANTAGE - Gives **sustained release** over a long period of **time** e.g. several months.

Dwg.0/0

TECH UPTX: 20010328

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Composition: Composition comprises:

(i) a peptide or a luteinizing hormone **releasing hormone** (LH-RH) compound (preferably of formula 5-oxo-Pro-His-Trp-Ser-Tyr-Y-Leu-Arg-Pro-Z (I);

(ii) 3-hydroxy-2-naphthoic acid or preferably 1-hydroxy-2-naphthoic acid; and

(iii) **lactic** acid-**glycolic** acid **polymer** having a mol ratio of 100/0-40/60 (preferably 100/0) % and a weight-average molecular weight of 3000-100000 (preferably 20000-50000).

Y = DLeu, DAla, DTrp, DSer(tBu), D2Nal or DHis(ImBzl); and

Z = NHEt or Gly-NH2.

L14 ANSWER 9 OF 25 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
AN 2000-505833 [45] WPIDS
CR 1994-248856 [30]
DNC C2000-151814
TI New polyester containing carboxy groups, useful for slow release of ionogenic amines, e.g. somatostatin, includes at least one hydroxypolycarboxylic acid.
DC A23 B04 B07
IN JACKSON, E A; MOREAU, J; SHALABY, S W; JACKSON, S A
PA (BIOM-N) BIOMEASURE TNC; (POLY-N) POLY-MED; (POLY-N) POLY-MED INC; (SCRC) SAS SOC CONSEILS RECH & APPL SCI; (SCRC) SOC CONSEILS RECH & APPL SCI; (SCRC) SCRAS SOC CONSEILS RECH & APPL SCI
CYC 91
PI WO 2000043435 A1 20000727 (200045)* EN 45p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ TZ UG ZW
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
AU 2000027362 A 20000807 (200055)
BR 2000007742 A 20011023 (200172)
EP 1159328 A1 20011205 (200203) EN
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI
CZ 2001002670 A3 20020213 (200221)
KR 2002001724 A 20020109 (200246)
CN 1344287 A 20020410 (200249)
MX 2001007537 A1 20011101 (200279)
JP 2002535426 W 20021022 (200301) 53p
JP 2003183364 A 20030703 (200352) 20p

NZ 513072 A 20031031 (200380)
JP 3476775 B2 20031210 (200382) 22p
AU 769658 B 20040129 (200412)

ADT WO 2000043435 A1 WO 2000-US1753 20000126; AU 2000027362 A AU 2000-27362 20000126; BR 2000007742 A BR 2000-7742 20000126, WO 2000-US1753 20000126; EP 1159328 A1 EP 2000-905719 20000126, WO 2000-US1753 20000126; CZ 2001002670 A3 WO 2000-US1753 20000126, CZ 2001-2670 20000126; KR 2002001724 A WO 2000-US1753 20000126, KR 2001-709428 20010726; CN 1344287 A CN 2000-803131 20000126; MX 2001007537 A1 MX 2001-7537 20010726; JP 2002535426 W JP 2000-594849 20000126, WO 2000-US1753 20000126; JP 2003183364 A Div ex JP 2000-594849 20000126, JP 2002-253916 20000126; NZ 513072 A NZ 2000-513072 20000126, WO 2000-US1753 20000126; JP 3476775 B2 JP 2000-594849 20000126, WO 2000-US1753 20000126; AU 769658 B AU 2000-27362 20000126

FDT AU 2000027362 A Based on WO 2000043435; BR 2000007742 A Based on WO 2000043435; EP 1159328 A1 Based on WO 2000043435; CZ 2001002670 A3 Based on WO 2000043435; KR 2002001724 A Based on WO 2000043435; JP 2002535426 W Based on WO 2000043435; NZ 513072 A Div in NZ 527337, Based on WO 2000043435; JP 3476775 B2 Previous Publ. JP 200235426, Based on WO 2000043435; AU 769658 B Previous Publ. AU 2000027362, Based on WO 2000043435

PRAI US 1999-237405 19990126

AB WO 200043435 A UPAB: 20040218

NOVELTY - Polyester (I) contains at least one carboxy group and has carboxy:hydroxy ratio over 1. (I) includes at least: (i) citric acid, epsilon -caprolactone (iC) and glycolide; or (ii) tartaric acid.

DETAILED DESCRIPTION - Polyester (I) contains at least one of L, D or DL-**lactic** acid; malic, tartaric or citric acids; epsilon -caprolactone (iC); p-dioxanone; epsilon -caproic acid; (cyclo)alkylene oxalate; alkylene succinate; beta -hydroxybutyrate; optionally substituted trimethylene carbonate (TMC); 1,5- or 1,4-dioxepan-2-one; glycolide; **glycolic** acid; L, D or DL-lactide; meso-lactide, or their optically active isomers, racemates or **copolymers.**

An INDEPENDENT CLAIM is also included for a composition containing (I) ionically conjugated to one or more bioactive peptides (II) comprising at least one ionogenic amine, with at least 50 weight% of (II) ionically conjugated to (I).

USE - (I) are used to conjugate biologically active peptides (II) for preparation of **sustained release** formulations.

ADVANTAGE - Conjugation of (I) and (II) provides release of (II) at predetermined rates, and therapeutic doses of (II) are maintained for at least 7 (preferably 20) days. The conjugates are easily injected to form microspheres/microparticles or implantable rods or films, without using multiphase emulsions or aqueous two-phase systems. (I) are biodegradable or absorbable and by appropriate choice of monomers can be tailored to have the required chemical reactivity for chain hydrolysis and maximum binding of (II).

A composition was prepared from (a) 800 mg 73.5:24.5:2 poly(L-lactide-co-glycolide/malic acid), acid number 1800, and (b) 200 mg of the D-Trp6 derivative of luteinizing-hormone **releasing hormone.** 50 mg of the product were placed in 5 ml phosphate-buffered saline (pH 7.27) and tested for peptide release. The percentage releases were 11, 53, 55 and 75% after 1, 7, 14 and 24 days, respectively.

Dwg.0/3

TECH UPTX: 20000918

TECHNOLOGY FOCUS - POLYMERS - Preferred Polymers: (I) of (i) have a ratio of iC:glycolide of 90:10 to 99:1 (especially 97:3). (I) of (ii) either comprises D or L-lactic acid and optionally also glycolide, or contains tartaric acid, iC and TMC, with an iC:TMC ratio of 90:10 to 99:1

(especially 98:2). Particularly (I) has a viscosity of 0.05-0.7 dl/g in chloroform and a molecular weight of 1200-40000.
Preparation: Particularly, (I) is prepared by (auto)catalyzed direct condensation between hydroxy acids in presence of polycarboxylic hydroxyacid, resulting in polymers that have acid-tipped hydroxy end groups. Other methods for producing (I) are e.g. ring-opening polymerization of lactones in presence of hydroxy-polycarboxylic acids and reaction of hydroxyacids with a cyclic dimer, then condensation in presence of polycarboxylic acid. (I) is reacted with (II) in liquid medium, particularly a mixture of aprotic solvent for (I), e.g. tetrahydrofuran, and water as solvent for (II), particularly used as a salt with a monocarboxylic acid having a pKa of at least 3.5.

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Peptides: Typical of many (II) are luteinizing-hormone **releasing hormone** (LHRH), somatostatin, calcitonin, glucagon, adrenocorticotrophic hormone, substance P etc., and their analogs and fragments. Especially preferred are the LHRH analog of formula pGlu-His-Trp-Ser-Tyr-D-Trp-Leu-Arg-Pro-Gly-NH2 (IIa) and the somatostatin analog of formula NH2-beta-D-Nal-Cys-Tyr-Trp-Lys-Val-Cys-Thr-NH2 (IIb), cyclized between the two Cys; beta-Nal = 2-naphthyl-alanine.
Preferred composition: This is a rod, coated with a layer of (absorbable) polyester, especially having the same composition as (I), and is produced by casting, pressing or extrusion. The composition contains 1-50 (particularly 10-20) wt.% (II), and at least 85 (particularly 99) % of (II) is ionically bound. The rate at which (II) is released is increased by: (1) decreasing the pKa difference between (I) and (II); (2) increasing the chemical reactivity of (I); (3) decreasing the density of (I); and (4) increasing matrix hydrophilicity.

L14 ANSWER 10 OF 25 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
AN 2000-303444 [26] WPIDS
CR 1999-277257 [23]
DNC C2000-092047
TI New biodegradable tri-block polymers with a molecular weight of 2000-4990 and reverse thermal gelation properties are useful for the **controlled release** administration of a drug.
DC A23 A25 A96 B04 B05 B07 D16
IN JEONG, B; RATHI, R C; ZENTNER, G M
PA (MACR-N) MACROMED INC
CYC 90
PI WO 2000018821 A1 20000406 (200026)* EN 41p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ TZ UG ZW
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG UZ VN YU ZA ZW
AU 2000010983 A 20000417 (200035)
US 6201072 B1 20010313 (200120)
NO 2001001639 A 20010330 (200137)
BR 9914258 A 20010703 (200141)
EP 1141079 A1 20011010 (200167) EN
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI
KR 2001083880 A 20010903 (200217)
CN 1324374 A 20011128 (200219)
JP 2002525404 W 20020813 (200267) 41p
NZ 510832 A 20021025 (200274)
AU 758475 B 20030320 (200329)

MX 2001003316 A1 20020401 (200363)

ADT WO 2000018821 A1 WO 1999-US22755 19990930; AU 2000010983 A AU 2000-10983 19990930; US 6201072 B1 CIP of US 1997-943167 19971003, CIP of US 1998-164865 19981001, US 1999-396589 19990915; NO 2001001639 A WO 1999-US22755 19990930, NO 2001-1639 20010330; BR 9914258 A BR 1999-14258 19990930, WO 1999-US22755 19990930; EP 1141079 A1 EP 1999-954698 19990930, WO 1999-US22755 19990930; KR 2001083880 A KR 2001-704062 20010330; CN 1324374 A CN 1999-812495 19990930; JP 2002525404 W WO 1999-US22755 19990930, JP 2000-572276 19990930; NZ 510832 A NZ 1999-510832 19990930, WO 1999-US22755 19990930; AU 758475 B AU 2000-10983 19990930; MX 2001003316 A1 WO 1999-US22755 19990930, MX 2001-3316 20010330

FDT AU 2000010983 A Based on WO 2000018821; US 6201072 B1 CIP of US 6004573, CIP of US 6117949; BR 9914258 A Based on WO 2000018821; EP 1141079 A1 Based on WO 2000018821; JP 2002525404 W Based on WO 2000018821; NZ 510832 A Based on WO 2000018821; AU 758475 B Previous Publ. AU 2000010983, Based on WO 2000018821; MX 2001003316 A1 Based on WO 2000018821

PRAI US 1999-396589 19990915; US 1998-164865 19981001; US 1997-943167 19971003

AB WO 200018821 A UPAB: 20031001

NOVELTY - A biodegradable ABA- or BAB-type tri-block polymer with an average molecular weight of 2000 to 4990 and reverse thermal gelation properties, comprising 51-83% polyester and 17-9% polyethylene glycol, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are included for the following:

(1) an aqueous biodegradable polymeric drug delivery composition with reverse thermal gelation properties comprising an aqueous phase containing a drug and the novel tri-block polymer; and

(2) a method for enhancing drug solubility comprising mixing the drug with the aqueous biodegradable polymeric drug delivery composition of (1).

USE - The polymer is useful for the **controlled release** administration of a drug, especially a polypeptide, protein, nucleic acid, gene, hormone, anti-cell proliferation agent, or anticancer agent (claimed).

ADVANTAGE - The polymer increases the solubility of many drug substances.

Dwg.0/4

TECH UPTX: 20000531

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Drugs: The drug is preferably oxytocin, vasopressin, adrenocoricotropic hormone, epidermal growth factor, platelet-derived growth factor, prolactin, luliberin, luteinizing hormone **releasing hormone** (LHRH), LHRH agonist, LHRH antagonist, growth hormone, growth hormone **releasing factor**, insulin, erythropoietin, somatostatin, glucagon, interleukin-2, interferon-alpha, -beta or -gamma, tetragastrin, pentagastrin, urogastrone, secretin, calcitonin, enkephalin, endorphin, angiotensin, thyrotopin **releasing hormone**, tumor necrosis factor, nerve growth factor, granulocyte-colony stimulating factor, granulocyte macrophage-colony stimulating factor, macrophage-colony stimulating factor, heparinase, bone morphogenic protein, hANP, glucagon-like peptide, interleukin-11, renin, bradykinin, bacitracins, polymyxin, colistin, tyrocidine, gramicidin, cyclosporin, enzyme, cytokine, antibody or vaccine.

Preferred composition: The aqueous composition contains an anticancer drug which is mitomycin, bleomycin, BCNU, carboplatin, doxorubicin, daunorubicin, methotrexate, paclitaxel, taxotere, actinomycin D, or camptothecin, or synthetic analogs, modifications or equivalents of them. The drug is present in the composition in the range 0.01-20% by weight.

TECHNOLOGY FOCUS - **POLYMERS** - Preferred Composition: The

polyester is preferably synthesized from D,L-lactide, D-lactide, L-lactide, D,L-**lactic** acid, D-**lactic** acid, L-**lactic** acid, glycolide, **glycolic** acid, eta-caprolactone, eta-hydroxyhexanoic acid, gamma-butyrolactone, gamma-hydroxybutyric acid, delta-valerolactone, delta-hydroxyvaleric acid, hydroxybutyric acid or malic acid. The A-block **polymer** preferably comprises 20-100mole% lactide and 0-80mole% glycolide. The hydrophobic A-block **polymer** preferably has an average molecular weight of 600-3000 and the hydrophilic B-block **polymer** preferably has an average molecular weight of 500-2200.

L14 ANSWER 11 OF 25 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
AN 2000-086567 [07] WPIDS
DNC C2000-024059
TI Drug delivery system for **controlled release** comprising drug conjugated to biodegradable polyester.
DC A23 A96 B07 C07
IN LEE, G H; NAM, Y S; OH, J E; PARK, T G; LEE, K H
PA (KOAD) KOREA ADV INST SCI & TECHNOLOGY; (MOGA-N) MOGAM BIOTECHNOLOGY RES INST; (KOAD) KOREA INST SCI & TECHNOLOGY; (LEEK-I) LEE K H; (NAMY-I) NAM Y S; (OHJE-I) OH J E; (PARK-I) PARK T G
CYC 22
PI WO 9959548 A1 19991125 (200007)* EN 70p
RW: AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE
W: JP US
KR 99085365 A 19991206 (200056)
EP 1082105 A1 20010314 (200116) EN
R: CH DE ES FR GB IT LI SE
JP 2002526383 W 20020820 (200258) 47p
US 6589548 B1 20030708 (200353)
US 2004013728 A1 20040122 (200407)
ADT WO 9959548 A1 WO 1999-KR243 19990514; KR 99085365 A KR 1998-17740 19980516; EP 1082105 A1 EP 1999-919701 19990514, WO 1999-KR243 19990514; JP 2002526383 W WO 1999-KR243 19990514, JP 2000-549213 19990514; US 6589548 B1 WO 1999-KR243 19990514, US 2000-700380 20001114; US 2004013728 A1 Cont of WO 1999-KR243 19990514, Cont of US 2000-700380 20001114, US 2003-423536 20030425
FDT EP 1082105 A1 Based on WO 9959548; JP 2002526383 W Based on WO 9959548; US 6589548 B1 Based on WO 9959548; US 2004013728 A1 Cont of US 6589548
PRAI KR 1998-17740 19980516
AB WO 9959548 A UPAB: 20000209
NOVELTY - **Sustained controlled release** system comprises drug molecules conjugated to a biodegradable polyester polymer via a covalent bond.

DETAILED DESCRIPTION - An INDEPENDENT CLAIM is included for production of the system which comprises:

(1) activating drug molecule or polymer by mixing with coupling agents, bases and optionally additives;

(2) conjugating drug molecule with polymer by adding drug molecule to the obtained activated polymer solution or by adding polymer to the activated drug molecule solution and

(3) purifying polymer molecule conjugate.

USE - Used for sustained delivery of biologically active molecules.

ADVANTAGE - The system gives a **sustained release** of active agent without an initial burst. High loading of hydrophilic drugs may be obtained and there is no requirement to remove the polymer carrier as it degrades into smaller molecules in the body and is eliminated.

Dwg.0/0
TECH UPTX: 20000209

TECHNOLOGY FOCUS - **POLYMERS** - Preferred materials: The biodegradable polyester **polymer** comprises **poly**(**lactic** acid), **poly**(**glycolic** acid), **poly**(D-**lactic** co-**glycolic** acid), **poly**(L-**lactic** co-**glycolic** acid), **poly**(L-**lactic** co-**glycolic** acid), **poly**(SD,L **lactic** co-**glycolic** acid), **poly**(caprolactone), **poly**(valerolactone), poly(hydroxybutyrate), poly(hydrovalerate), polydioxnanone or their derivatives. The **polymer** is a **poly**(**lactic**-co-**glycolic** acid) with a ratio of **lactic** to **glycolic** acids of 1:10-10:1. The molecular weight of the **polymer** is 1000-100000 Da.

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preferred Methods: Conjugation of the drug to polymer is effected via a covalent bond e.g. via an ester, amide, anhydride, carbonate, imine, thioester, urea, urethane, disulphide or carbamate bond. The coupling is direct or via an additional group such as a bridge, spacer or linkage group.

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred components: The drug comprises a peptide, protein, therapeutic agent, diagnostic agent or non biological material e.g. pesticides, herbicides or fertilizers. The peptide comprises insulin, hormones, calcitonin, ACTH, glucagon, somatostatin, somatotropin, somatomedin, parathyroid hormone, erythropoietin, hypothalmic **releasing factor**, prolactin, thyroid stimulating hormone, endorphins, enkephalins, vasopressin, non naturally occurring opioids, superoxide dismutase, interferon, asparaginase, arginase, arginine deaminase, adenosine deaminase ribonuclease, trypsin, chemotrypsin or pepsin. The therapeutic agent comprises anticancer agents, antibiotics, anticoagulants, germicides, antiarrhythmic agents or their prodrugs or derivatives.
Preferred Formulation: The system is formulated into microspheres of 1-300 mum in size, nanoparticles of 50-1000 nm in size or films.

L14 ANSWER 12 OF 25 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
AN 1999-494044 [41] WPIDS
DNC C1999-144752
TI Microparticle of absorbable, heterochain polymer carrying immobilized protein or peptide, providing **controlled, sustained release.**
DC A96 A97 B04
IN SHALABY, S W
PA (POLY-N) POLY-MED INC
CYC 84
PI WO 9938536 A1 19990805 (199941)* EN 53p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG ZW
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZW
AU 9923291 A 19990816 (200002)
NO 2000003810 A 20000913 (200058)
EP 1053020 A1 20001122 (200061) EN
R: AT BE CH DE DK ES FI FR GB GR IE IT LI LU NL PT SE
CZ 2000002654 A3 20001213 (200103)
CN 1289256 A 20010328 (200140)
HU 2001001250 A2 20010828 (200157)
JP 2002501908 W 20020122 (200211) 62p

ADT WO 9938536 A1 WO 1999-US1180 19990120; AU 9923291 A AU 1999-23291 19990120; NO 2000003810 A WO 1999-US1180 19990120, NO 2000-3810 20000725; EP 1053020 A1 EP 1999-903216 19990120, WO 1999-US1180 19990120; CZ 2000002654 A3 WO 1999-US1180 19990120, CZ 2000-2654 19990120; CN 1289256 A CN 1999-802517 19990120; HU 2001001250 A2 WO 1999-US1180 19990120, HU 2001-1250 19990120; JP 2002501908 W WO 1999-US1180 19990120, JP 2000-529268 19990120

FDT AU 9923291 A Based on WO 9938536; EP 1053020 A1 Based on WO 9938536; CZ 2000002654 A3 Based on WO 9938536; HU 2001001250 A2 Based on WO 9938536; JP 2002501908 W Based on WO 9938536

PRAI US 1998-15394 19980129

AB WO 9938536 A UPAB: 19991011

NOVELTY - Microparticle (A) comprises an absorbable, heterochain polymer core (I) and at least one peptide and/or protein (II) immobilized on (I).

DETAILED DESCRIPTION - (I) is:

(i) growth hormone (GH) **releasing peptide**, luteinizing **hormone releasing hormone** (LHRH), somatostatin, bombesin, gastrin-**releasing peptide**, calcitonin, bradykinin, galanin, melanocyte stimulating hormone, GH **releasing factor**, amylin, tachykinins, secretin, parathyroid hormone (PTH), enkephalin, endothelin, calcitonin gene **releasing peptide**, neuromedins, PTH-related peptide, glucagon, neurotensin, adrenocorticotrophic hormone, peptide YY, glucagon-**releasing peptide**, vasoactive intestinal peptide, pituitary adenylate cyclase activating peptide, motilin, substance P, neuropeptide Y, thyroid stimulating hormone and their analogs, fragments or salts, or

(ii) GH, erythropoietin, granulocyte(-macrophage) colony stimulating factors or interferons.

INDEPENDENT CLAIMS are also included for the following:

(1) encased microparticles (A') comprising one or more (A) encased within an absorbable encasing polymer (III);

(2) a therapeutic composition comprising (A) or (A') and a carrier; and

(3) preparation of (A') by encasing a bound (A) with (I).

ACTIVITY - None given.

MECHANISM OF ACTION - None given.

USE - (A) provide **controlled** and **sustained release** of (II), most particularly analogs of luteinizing hormone **releasing hormone** (LHRH) and somatostatin. Particles (mean diameter 122.14 microns m) containing 5.38wt.% of the LHRH analog pyroGlu-His-Trp-Ser-Tyr-D-Trp-Leu-Arg-Pro-Gly-NH2 (A) was prepared in 7:1 **poly(glycolic** acid-citric acid) particles, then encased in 75:25 poly(L-lactide co-glycolide), initiated with propanediol, with peptide-loaded polymer to encasing polymer weight ratio 1:1. The particles, amount not specified, were injected intramuscularly into rats; this treatment provided a plasma level of over 150 pg/ml (A) for 20 days and kept the plasma level of testosterone below 1 ng/ml for 21 days.

ADVANTAGE - Complex formation between (I) and (II) is mainly a surface phenomenon, rather than formation of a well-defined chemical conjugate.

Dwg.0/0

TECH UPTX: 19991105

TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preferred Peptides: The peptides are: (a) the LHRH analog pyroGlu-His-Trp-Ser-Tyr-D-Trp-Leu-Arg-Pro-Gly-NH2 (A), or

(b) three somatostatin analogs, e.g. N-(hydroxyethylpiperazinyl-acetyl)-D-Phe-Cys-Tyr-D-Trp-Lys-aminobutyric acid-Cys-Thr-NH2.

TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Particles: (II) is 0.1-30 wt.% of (A). (I) comprises glycolate, optionally also citrate, tartrate or

malate units, with ratio glycolate: other acid units 7-20:1. The glycolate residues may end in carboxy or amino groups. (III) preferably contains:
(a) D,L-lactide, optionally also L-lactide, units, or
(b) D,L- and L-lactide units, plus glycolide units, particularly with ratios D,L-lactide :glycolide 75:25 to 90:10, or L-lactide to D,L-lactide 80:20.
(III) is 5-70, preferably 30-50, wt.% of (A'). (II) is immobilized on carboxy or amino groups present in (I); the amino groups are particularly introduced by amidation with a diamine. (A) preferably have diameter 0.5-100, especially 3-10, mum.
Preferred Compositions: The compositions may also include a non-aqueous, absorbable, gel-forming liquid polyester (IV) to provide further **control** over **release** of (II).
Preferred Active Ingredient: (II) is an LHRH or somatostatin analog.
Preparation: To produce (A'), a dispersion of (A) in a solution of (III) is dropped into a pre-cooled medium that is not a solvent for (III). Particularly the solution contains 5-30% (III) and the medium is an alcohol of over 2C atoms, cooled at room temperature to -80degreesC. Preferred is 2-propanol cooled to -60 to -80degreesC. Alternatively, (A) are encased in (III) using an emulsion technique. To produce (A), microparticles, in sodium salt form, are incubated with an aqueous solution of (II) in free base form.

TECHNOLOGY FOCUS - POLYMERS - (I) comprise glycolate, optionally also citrate, malate or tartrate units. (III) preferably contains:
(i) D,L-lactide, optionally also L-lactide, units, or
(ii) D,L- and L-lactide units, plus glycolide units, particularly with ratios D,L-lactide :glycolide 75:25 to 90:10 or L-lactide to D,L-lactide 80:20. A typical (IV) is a block copolymer of 80% trimethylene carbonate-glycolide (60:40) and 20% poly(ethylene glycol) 400.

L14 ANSWER 13 OF 25 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
AN 1998-008591 [01] WPIDS
DNN N1998-006790 DNC C1998-003009
TI Composition comprising biodegradable copoly(lactic/glycolic acid) - used for producing solid implant in situ in mammalian body, useful for bioactive agent **controlled release.**
DC A23 A96 B07 C07 D22 P34
IN ELIAZ, R; KOST, J
PA (UYNE) UNIV BEN-GURION NEGEV
CYC 76
PI WO 9742987 A1 19971120 (199801)* EN 62p
RW: AT BE CH DE DK EA ES FI FR GB GH GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE GH HU IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK TJ TM TR TT UA UG US UZ VN YU
AU 9726494 A 19971205 (199814)
US 6206920 B1 20010327 (200119)
ADT WO 9742987 A1 WO 1997-IL154 19970508; AU 9726494 A AU 1997-26494 19970508; US 6206920 B1 WO 1997-IL154 19970508, US 1998-180500 19981223
FDT AU 9726494 A Based on WO 9742987; US 6206920 B1 Based on WO 9742987
PRAI IL 1996-118235 19960513
AB WO 9742987 A UPAB: 19980107
Composition, comprises a mixture of: (a) **poly(lactic** -co-**glycolic** acid) (PLGA) **copolymer**, containing 10-100 (preferably 50-90) weight% **lactic** acid (LA) units; and (b) alpha -(tetrahydrofuranyl)- omega -hydroxy-poly(oxy-1,2-ethanediyl) (glycofurol, ethoxylated tetrahydrofurfuryl alcohol). Also claimed is a method of producing a solid implant in situ, in a mammalian body, comprising: (i)

preparing a composition as above by dissolving (a) in (b); (ii) administering the composition; and (iii) allowing the glycofurol to dissipate in the mammal, leaving a solid implant composed of a PLGA **polymeric** matrix.

USE - The composition, with optional addition of bioactive agents, is used to form biological implants in situ, by contact with an aqueous fluid. After administration, the glycofurol dissipates, leaving a solid implant of PLGA matrix. These can be used for tissue regeneration and space filling after tissue removal, e.g., a tumour; for bone replacement and where ingrowth into a space is desired; as a prosthetic or orthodontic implant; and, with addition of bioactive agents to the composition, for their **controlled release** (all claimed). A wide variety of agents, of use in both medical and veterinary practice can be delivered in this way, including e.g. insulin or other hormones, growth factors, interferon, cytokines, cytokine binding proteins, or luteinising hormone **releasing hormone** (LH-RH); oligo- or polynucleotides, steroids, contraceptives, hormone antagonists, prostaglandins, antiarrhythmics, antiinflammatory, and anticancer agents.

ADVANTAGE - Glycofurol is acceptable pharmacologically in limited amounts. The composition is liquid enough to be injected through a needle to the desired site, avoiding surgery, surgery for removal of the implant is also unnecessary, as the implant is biodegradable (claimed).
Dwg.0/18

L14 ANSWER 14 OF 25 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
AN 1994-341448 [42] WPIDS
DNC C1994-155477
TI Bio-erodable material for continuous drug **release** - comprises polymer of **controlled** density impregnated with drug solution or extruded with solid drug.
DC A96 B07
IN GRESSER, J D; TRANTOLO, D J; WISE, D L
PA (CAMB-N) CAMBRIDGE SCI INC
CYC 19
PI WO 9423698 A1 19941027 (199442)* 33p
RW: AT BE CH DE DK ES FR GB GR IE IT LU MC NL PT SE
W: JP
US 5456917 A 19951010 (199546) 10p
EP 693923 A1 19960131 (199609) EN
R: AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE
EP 693923 A4 19960821 (199702)
JP 08512288 W 19961224 (199710) 30p
EP 693923 B1 20001025 (200055) EN
R: AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE
DE 69426196 E 20001130 (200102)
ES 2152992 T3 20010216 (200114)
ADT WO 9423698 A1 WO 1994-US3710 19940405; US 5456917 A CIP of US 1993-45917 19930412, US 1994-180914 19940112; EP 693923 A1 EP 1994-928680 19940405, WO 1994-US3710 19940405; EP 693923 A4 EP 1994-928680 ; JP 08512288 W JP 1994-523272 19940405, WO 1994-US3710 19940405; EP 693923 B1 EP 1994-928680 19940405, WO 1994-US3710 19940405; DE 69426196 E DE 1994-626196 19940405, EP 1994-928680 19940405, WO 1994-US3710 19940405; ES 2152992 T3 EP 1994-928680 19940405
FDT EP 693923 A1 Based on WO 9423698; JP 08512288 W Based on WO 9423698; EP 693923 B1 Based on WO 9423698; DE 69426196 E Based on EP 693923, Based on WO 9423698; ES 2152992 T3 Based on EP 693923
PRAI US 1993-45917 19930412; US 1994-180914 19940112
AB WO 9423698 A UPAB: 19941212
Bioerodible particle for continuous release of a medicament (I) is made by (1) grinding a bioerodible polymer (A) of adjusted density, and sorting to

select particles (with pores) of particular size; (2) suspending these particles in a soln.of (I) in a solvent that does not dissolve (A); (3) applying vacuum to the suspension to remove air; (4) releasing vacuum to load the pores with solution and (5) recovering the loaded particles. Alternatively, the (A) particles are blended with dry (I) and the mixture extruded to a rod at specified temperature and pressure.

USE - The method is exemplified for slow release of isoniazide (antitubercular); naltrexone (narcotic antagonist); luteinising hormone-**releasing hormone** analogue (treatment of prostatic adenocarcinoma) or IL-2 (treatment of cancer or AIDS).

ADVANTAGE - The materials are prepared without solvent and the rate of **release** can be **controlled** by particle size (faster **release** from smaller particles) and/or extrusion pressure (high pressure gives slower release).

Dwg.5/5

L14 ANSWER 15 OF 25 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
AN 1993-029170 [08] WPIDS
CR 1993-029127 [04]
DNC C1993-013056
TI Compsn. for **sustained release** of new luteinising hormone **releasing hormone** analogues - incorporated as water insoluble salt into microspheres of biodegradable polymer.
DC A96 B04 B07
IN HEIMGARTNER, F; ORSOLINI, P; ORSOLINO, P
PA (DEBI-N) DEBIO RECH PHARM SA; (ASTA) ASTA MEDICA AG
CYC 6
PI

GB 2257973	A	19930127 (199304)*		15p
LU 88150	A	19930215 (199312)	FR	
LU 88151	A	19930215 (199312)	FR	
NO 9202885	A	19930125 (199312)		
NO 9202886	A	19930125 (199312)		
SE 9202212	A	19930123 (199312)		
SE 9202213	A	19930123 (199312)		
FR 2679450	A1	19930129 (199313)		17p
FI 9203320	A	19930123 (199316)		
FI 9203321	A	19930123 (199316)		
GB 2257973	B	19960228 (199612)		

ADT GB 2257973 A GB 1992-15480 19920721; LU 88150 A LU 1992-88150 19920721; LU 88151 A LU 1992-88151 19920721; NO 9202885 A NO 1992-2885 19920721; NO 9202886 A NO 1992-2886 19920721; SE 9202212 A SE 1992-2212 19920721; SE 9202213 A SE 1992-2213 19920721; FR 2679450 A1 FR 1992-8991 19920721; FI 9203320 A FI 1992-3320 19920721; FI 9203321 A FI 1992-3321 19920721; GB 2257973 B GB 1992-15480 19920721
PRAI CH 1991-2178 19910722
AB GB 2257973 A UPAB: 19930924
Compsn. for **sustained** and **controlled release** of the peptide (I) comprises microspheres of polymeric biodegradable material (A) which include a water-insoluble salt of formula Ac-D-Nal-D-pClPhe-R3-Ser -Tyr-D-Cit-Leu-Arg-Pro -D-Ala-NH2 (I) where D-Nal = D-3-(2-naphthyl)alanine; D-Cit = D-citrulline; R3 = D-Trp or D-Pal(D-3-(3-pyridyl)alanine). Also new are (I) and their water-insoluble salts.

Specifically, (I) salts are the pamoate, tannate, stearate or palmitate and (A) is a (co)**polymer** of **lactic** and/or **glycolic** acids.

USE/ADVANTAGE - (I) are LHRH analogues useful for treating hormone-dependent disorders. In these compsns. they are **released** at a **sustained** rate over several days following parenteral admin. Microspheres of exactly controlled size can be made with high (up

to 20 weight%) loading of (I) salt and with good yield of peptide incorporation.
0/0

L14 ANSWER 16 OF 25 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
AN 1992-427153 [52] WPIDS
CR 1991-247334 [34]; 1992-316444 [39]
DNC C1992-189539
TI Long releasing microcapsule containing physiologically active polypeptide - obtd. by microencapsulating water-in-oil emulsion, containing inner water phase solution containing polypeptide and oil phase solution, etc..
DC A96 B04 B07
PA (TAKE) TAKEDA CHEM IND LTD
CYC 1
PI JP 04321622 A 19921111 (199252)* 7p
JP 2653255 B2 19970917 (199742) 7p
ADT JP 04321622 A JP 1991-32302 19910131; JP 2653255 B2 JP 1991-32302 19910131
FDT JP 2653255 B2 Previous Publ. JP 04321622
PRAI JP 1990-33133 19900213; JP 1991-8896 19910129
AB JP 04321622 A UPAB: 19931006
Preparation involves encapsulating a water-in-oil emulsion consisting of an inner water phase solution containing about 20-70 weight% of a physiologically active polypeptide(s) and an oil phase solution containing, as **release control** substance, a **copolymer**(s) or a **homopolymer**(s) of a **lactic/glycolic** ratio of 80/20 to 100/0 and a weight average molecular weight of 7,000-30,000. It is capable of releasing the polypeptide over a period of 2 months or longer.
The peptides usually have a molecular weight of 200-100,000. Available peptides include luteinising hormone **releasing hormones** and their analogues. Their content in the microcapsule is usually 0.01-50 weight%, pref. 0.1-30 weight%. The polymer is most pref. the homopolymer of DL-lactic acid and pref. contains no polymerisation catalysts. Available solvents for the oil phase include dichloromethane, chloroethane, ethyl acetate, ethyl ether and/or benzene.
USE/ADVANTAGE - The microcapsule releases physiologically active peptides continuously over a period of 2 months or more.
0/0

L14 ANSWER 17 OF 25 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
AN 1992-316444 [39] WPIDS
CR 1991-247334 [34]; 1992-427153 [52]
DNC C1992-140605
TI Microcapsules for long term polypeptide release - comprises encapsulated water-in-oil emulsion containing biodegradable polymer.
DC A96 B04 B07 P33
IN INOUE, Y; OGAWA, Y; OKADA, H
PA (TAKE) TAKEDA CHEM IND LTD
CYC 4
PI AU 9181794 A 19920806 (199239)* 26p
BR 9103553 A 19920929 (199244)
NZ 239381 A 19921223 (199308)
AU 645108 B 19940106 (199408)
MX 183802 B 19970117 (199816)
ADT AU 9181794 A AU 1991-81794 19910812; BR 9103553 A BR 1991-3553 19910819; NZ 239381 A NZ 1991-239381 19910813; AU 645108 B AU 1991-81794 19910812; MX 183802 B MX 1991-721 19910819
FDT AU 645108 B Previous Publ. AU 9181794
PRAI JP 1991-32302 19910131
AB AU 9181794 A UPAB: 19971006
Production of a microcapsule, designed for zero order release of a

physiologically active polypeptide over a period of at least 2 months, comprises: (a) preparation of a water in oil (W/O) emulsion, having inner aqueous phase containing 20-70% w/w of the polypeptide and an oil phase containing a **copolymer** or **homopolymer** of average mol.weight 7000-30000, and a **lactic/glycolic** acid ratio of 80:20 - 100:0; and (b) subjecting the W/O emulsion to encapsulation.

Polypeptides with at least two amino acids and mol.weight 200-100000 are pref. employed. They include luteinising hormone **releasing hormone** (LH-RH) or water soluble analogues with mol.weight of at least 1000, e.g. TAP-144, (pyr)-Glu-His-Trp-Ser- Tyr-D-Leu-Leu-Arg-ProNHEt, or thyrotropin **releasing hormone** (TRH) (all claimed).

USE/ADVANTAGE - The microcapsules are easily admin. as injections and implants, i.m., s.c., i.v., or at an organ, joint cavity, or lesion (e.g. a tumour). They avoid the necessity for frequent attention to a patient, e.g. a daily injection, and the rate of **release** is **controlled** by the mol.weight of the **polymer** and the **lactic/glycolic** ratio. They also avoid the need for drug retaining substacnes, as used in prior art, although a drug retaining substance can be opt. added to the aqueous phase. The microcapsule provides stady **release** of the drug over **time** without undesirable initial ''burst'', or underdosing until impregnation or decomposition of the coating matrix is steady or has started. The **polymer** used is biodegradable, leaving no residues at the end of treatment

Dwg.0/0

L14 ANSWER 18 OF 25 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
AN 1992-133995 [17] WPIDS
DNC C1992-062653
TI Prolonged release biodegradable polymer for drug admin. - comprise poly-lactide blend with copolymer of hydroxy acid, provides constant drug release rate.
DC A96 B04 B07 C03 C07
IN ISHIGURO, S; OGAWA, Y; YAMADA, M; SEIKO, I; YASUAKI, O
PA (TAKE) TAKEDA CHEM IND LTD
CYC 28
PI EP 481732 A 19920422 (199217)* EN 13p
R: AT BE CH DE DK ES FR GB GR IT LI LU NL SE
NO 9104032 A 19920421 (199225)
AU 9185864 A 19920430 (199226)
CA 2053468 A 19920417 (199227)
FI 9104865 A 19920417 (199230)
PT 99236 A 19920930 (199245)
CN 1060851 A 19920506 (199303)
NZ 240214 A 19930225 (199312)
JP 05112468 A 19930507 (199323) 9p
ZA 9108168 A 19930630 (199331) 29p
AU 644019 B 19931202 (199404)
US 5304377 A 19940419 (199415) 8p
EP 481732 B1 19950301 (199513) EN 16p
R: AT BE CH DE DK ES FR GB GR IT LI LU NL SE
DE 69107773 E 19950406 (199519)
ES 2069221 T3 19950501 (199524)
IE 66705 B 19960124 (199613)
CN 1116212 A 19960207 (199741)
NO 302481 B1 19980309 (199817)
FI 101454 B1 19980630 (199834)
RU 2103005 C1 19980127 (199839)

PH 28606 A 19941121 (199840)
KR 199119 B1 19990615 (200059)
JP 3196035 B2 20010806 (200147) 9p
CA 2053468 C 20020709 (200254) EN

ADT EP 481732 A EP 1991-309490 19911015; NO 9104032 A NO 1991-4032 19911014; AU 9185864 A AU 1991-85864 19911015; CA 2053468 A CA 1991-2053468 19911015; FI 9104865 A FI 1991-4865 19911015; PT 99236 A PT 1991-99236 19911015; CN 1060851 A CN 1991-109723 19911016; NZ 240214 A NZ 1991-240214 19911014; JP 05112468 A JP 1991-267929 19911016; ZA 9108168 A ZA 1991-8168 19911014; AU 644019 B AU 1991-85864 19911015; US 5304377 A Cont of US 1991-777170 19911016, US 1992-986299 19921207; EP 481732 B1 EP 1991-309490 19911015; DE 69107773 E DE 1991-607773 19911015, EP 1991-309490 19911015; ES 2069221 T3 EP 1991-309490 19911015; IE 66705 B IE 1991-3624 19911016; CN 1116212 A Div ex CN 1991-109723 19911016, CN 1995-102413 19911016; NO 302481 B1 NO 1991-4032 19911014; FI 101454 B1 FI 1991-4865 19911015; RU 2103005 C1 SU 1991-5010042 19911015; PH 28606 A PH 1991-43292 19911014; KR 199119 B1 KR 1991-18235 19911016; JP 3196035 B2 JP 1991-267929 19911016; CA 2053468 C CA 1991-2053468 19911015

FDT AU 644019 B Previous Publ. AU 9185864; DE 69107773 E Based on EP 481732; ES 2069221 T3 Based on EP 481732; NO 302481 B1 Previous Publ. NO 9104032; FI 101454 B1 Previous Publ. FI 9104865; JP 3196035 B2 Previous Publ. JP 05112468

PRAI JP 1990-278037 19901016; JP 1991-217045 19910828

AB EP 481732 A UPAB: 19931006

A polymer for a prolonged release preparation comprises (a) 10-90% of a **polylactic** acid; and (b) 90-10% of a copolymer of glycolic acid and a hydroxycarboxylic acid of formula (I) HOCHR1COOH (I) where R= 2-8C alkyl. The **polylactic** acid is ka copolymer of D-and L-forms, with a mole ratio D/L of 45:55 to 25:75, and has a molecular weight peak value of 5000-30000, determined by gel permeation chromatography (GPC). (I) in the copolymer is 2-hydroxybutyric, 2-hydroxyvaleric, 2-hydroxy-3-methylbutyric, 2-hydroxycaproic, 2-hydroxyisocaproic, or 2-hydroxycaprylic acid. The proportion of glycolic acid/(I) is 40:60 to 70:30 mole%, and the copolymer has a molecular weight peak of 5000-20000 by GPC.

USE/ADVANTAGE - The polymer is biodegradable and can be used for formulations for pharmaceutical prepns. e.g. microcapsules. The period of drug **release** is **controlled** by use of a simple blend of slowly and rapidly degrading polymers. The drug is released at a constant rate, without an initial ''burst'', or poor or en masse release in the later stages, and the period can be over several weeks. A wide variety of drugs can be formulated, for admin. to various animals (mouse, rat, rabbit, sheep, pig, cow, horse, and humans), and is of partic. use for water soluble drugs, e.g. physiologically active polypeptide. An example is luteinising hormone-**releasing hormone** (LH-RH) or its functional analogues e.g. (II) or (III):

(Pyr(Glu-R1-Trp-Ser-R2-R3-R4-Arg-Pro-R5 (II)

(Pyr)Glu-His-Trp-Ser-Trp-D-Leu-Leu-Arg-Pro NHEt (III)

R1= His, Tyr, Trp, or p-NH2Phe; R2= Tyr or Phe; R3= Gly or a D-amino acid residue; R4= Leu, Ile, or Nle; R5= Gly-NH-R6 or NHR6; and R6= H or lower alkyl (opt. substd. with OH). (O/O)

O/O

L14 ANSWER 19 OF 25 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
AN 1992-026227 [04] WPIDS
DNC C1992-011275
TI Drug delivery system for **controlled release** proteins or polypeptide(s) - using hydrophobic biodegradable polyester polymer physically interacting with protein or polypeptide.
DC A96 B04 B07

IN DELUCA, P P
PA (KENT) UNIV KENTUCKY RES FOUND; (KENT) UNIV KENTUCKY RES; (DELU-I) DELUCA P P
CYC 25
PI EP 467389 A 19920122 (199204)* 22p
R: AT BE CH DE ES FR GB GR IT LI LU NL SE
NO 9102769 A 19920120 (199212)
AU 9180466 A 19920123 (199214)
CA 2046830 A 19920120 (199215)
FI 9103455 A 19920120 (199217)
ZA 9105584 A 19920429 (199223) 48p
PT 98397 A 19920529 (199227)
CS 9102248 A2 19920318 (199241)
JP 05103838 A 19930427 (199321) 18p
NZ 238951 A 19941222 (199505)
AU 656897 B 19950223 (199515)
EP 467389 A3 19940202 (199518)
NO 304411 B1 19981214 (199905)
EP 467389 B1 19991006 (199946) EN
R: AT BE CH DE DK ES FR GB GR IT LI LU NL SE
DE 69131677 E 19991111 (199954)
ES 2138584 T3 20000116 (200011)
CA 2046830 C 19991214 (200018) EN
FI 104954 B1 20000515 (200031)
US 6306406 B1 20011023 (200165)
US 2002051808 A1 20020502 (200234)#
MX 208498 A 20020621 (200369)
ADT EP 467389 A EP 1991-112118 19910719; ZA 9105584 A ZA 1991-5584 19910717; PT 98397 A PT 1991-98397 19910719; CS 9102248 A2 CS 1991-2248 19910719; JP 05103838 A JP 1991-179588 19910719; NZ 238951 A NZ 1991-238951 19910712; AU 656897 B AU 1991-80466 19910716; EP 467389 A3 EP 1991-112118 19910719; NO 304411 B1 NO 1991-2769 19910715; EP 467389 B1 EP 1991-112118 19910719; DE 69131677 E DE 1991-631677 19910719, EP 1991-112118 19910719; ES 2138584 T3 EP 1991-112118 19910719; CA 2046830 C CA 1991-2046830 19910711; FI 104954 B1 FI 1991-3455 19910717; US 6306406 B1 Cont of US 1990-554427 19900719, Cont of US 1991-716763 19910619, Cont of US 1992-865657 19920407, US 1995-481155 19950607; US 2002051808 A1 Cont of US 1995-481155 19950607, US 2001-944369 20010904; MX 208498 A MX 1991-249 19910717
FDT AU 656897 B Previous Publ. AU 9180466; NO 304411 B1 Previous Publ. NO 9102769; DE 69131677 E Based on EP 467389; ES 2138584 T3 Based on EP 467389; FI 104954 B1 Previous Publ. FI 9103455
PRAI US 1990-554427 19900719; US 1991-716763 19910619; US 1992-865657 19920407; US 1995-481155 19950607; US 2001-944369 20010904
AB EP 467389 A UPAB: 19931006
System comprising a hydrophobic biodegradable polymer and a protein or polypeptide. Physical interaction is between the polymer and protein or polypeptide so protection and **controlled release** of the protein or polypeptide is obtd. in vivo; the polymer may be a polyester, e.g. **polyglycolic** or **polylactic**-acid or a copolymer of glycolide and L-lactide, a polyorthoester or a polyanhydride; oral drug delivery system comprises hydrophobic biodegradable polymer and a protein or polypeptide. Physical interaction is between the polymer and protein or polypeptide, etc.

USE/ADVANTAGE - Stable formulation for protection and **controlled release** of the polypeptide or protein in vivo. Used for delivering e.g. calcitonin, insulin, angiotensin, vasopressin, desmopressin, LHRH, somatostatin, glucagon, somatomedin, oxytocin, gastrin, secretin, human atrial natriuretic polypeptide, adrenocorticotropic- or melanocyte stimulating-hormone, beta-endorphin, muramyl dipeptide, enkephalin, neurotensin, bombesin, VIP, CCK-8,

parathyroid hormone, endothelin, thyroid **releasing**- or growth-**hormone** or lymphokines.
0/7

L14 ANSWER 20 OF 25 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
AN 1991-247334 [34] WPIDS
CR 1992-316444 [39]; 1992-427153 [52]
DNC C1991-107320
TI Prolonged release microcapsule containing polypeptide drug - obtd. from water-in-oil emulsion containing polypeptide in aqueous phase and lactic acid (co)polymer in oil phase.
DC A96 B04 B07
IN INOUE, Y; OGAWA, Y; OKADA, H
PA (TAKE) TAKEDA CHEM IND LTD
CYC 24
PI EP 442671 A 19910821 (199134)*
R: AT BE CH DE ES FR GB GR IT LI LU NL SE
HU 56268 T 19910828 (199138)
NO 9100555 A 19910814 (199142)
CA 2036089 A 19910814 (199143)
FI 9100674 A 19910814 (199143)
PT 96727 A 19911031 (199148)
CN 1054009 A 19910828 (199222)
HU 206986 B 19930301 (199313)
EP 442671 A3 19920902 (199338)
RU 2018306 C1 19940830 (199516) 8p
EP 442671 B1 19950607 (199527) EN 11p
R: AT BE CH DE DK ES FR GB GR IT LI LU NL SE
DE 69110150 E 19950713 (199533)
ES 2073117 T3 19950801 (199537)
US 5480656 A 19960102 (199607) 7p
FI 96278 B 19960229 (199613)
IE 68436 B 19960612 (199641)
US 5643607 A 19970701 (199732) 6p
NO 301405 B1 19971027 (199750)
RU 2098121 C1 19971210 (199831) 9p
US 5814342 A 19980929 (199846)
CA 2316159 A1 19910814 (200058) EN
KR 194827 B1 19990615 (200059)
CA 2036089 C 20001205 (200101) EN
ADT EP 442671 A EP 1991-301053 19910211; CN 1054009 A CN 1991-101017 19910212; HU 206986 B HU 1991-475 19910213; EP 442671 A3 EP 1991-301053 19910211; RU 2018306 C1 SU 1991-4894792 19910212; EP 442671 B1 EP 1991-301053 19910211; DE 69110150 E DE 1991-610150 19910211, EP 1991-301053 19910211; ES 2073117 T3 EP 1991-301053 19910211; US 5480656 A Cont of US 1991-649727 19910201, US 1994-188918 19940131; FI 96278 B FI 1991-674 19910212; IE 68436 B IE 1991-474 19910212; US 5643607 A Cont of US 1991-649727 19910201, Div ex US 1994-188918 19940131, US 1995-458679 19950602; NO 301405 B1 NO 1991-555 19910212; RU 2098121 C1 Div ex SU 1991-4894792 19910212, RU 1993-34781 19930629; US 5814342 A Cont of US 1991-649727 19910201, Div ex US 1994-188918 19940131, Div ex US 1995-458679 19950602, US 1997-806954 19970226; CA 2316159 A1 Div ex CA 1991-2036089 19910211, CA 1991-2316159 19910211; KR 194827 B1 KR 1991-2509 19910213; CA 2036089 C CA 1991-2036089 19910211
FDT HU 206986 B Previous Publ. HU 56268; DE 69110150 E Based on EP 442671; ES 2073117 T3 Based on EP 442671; US 5643607 A Div ex US 5480656; NO 301405 B1 Previous Publ. NO 9100555; US 5814342 A Div ex US 5480656, Div ex US 5643607
PRAI JP 1990-33133 19900213
AB EP 442671 A UPAB: 20001230

A microcapsule designed for zero order release of a physiologically active polypeptide over a period of at least two months is claimed, where is produced by prepg a water-in-oil emulsion comprising an inner aq phase contg 20-708 wt% of the polypeptide and an oil phase contg a **copolymer** or **homopolymer** having a wt ave mol wt of 7,000-30,000 and molar compsn ratio of **lactic** acid/ **glycolic** acid of 80/20-100/0, then subjecting the water-in-oil emulsion to microencapsulation.

USE/ADVANTAGE - Useful for **sustained release** of eg luteinising hormone- **release** hormone (LH-RH) and its analogues, LH-RH antagonists, prolactin, ACTH, melanocyte-stimulating hormone (MSH), thyrotropin-**releasing hormone** (TRH), thyroid-stimulating hormone (TSH), luteinising hormone (LH), follide-stimulating hormone (FSH), vasopressin or derivs, oxytocin, calcitomin, parathyroid hormone (PTH) and derivs, glucagon, gastrin, vasoactive intestinal peptide (IVP), lipocortin, vasocortin, atrial natriuretic peptide (ANP), HCG) insulin, growth factors, interferons interleukins, TBF, CSG, EP0, t-PA, blood coagulation factors, polymixin B, bacitracin, etc. @(9pp Dwg.No.0/0)

L14 ANSWER 21 OF 25 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
AN 1991-087633 [13] WPIDS
DNC C1991-037233
TI Reduction of solvent content of polymer-drug microcapsules - containing hormonally
active, water-soluble polypeptide, by contact with pressurised gas.
DC A35 A96 B04
IN LOKENSGARD, D M
PA (SYNT) SYNTEX (USA) INC; (SYNT) SYNTEX USA INC
CYC 16
PI CA 2020755 A 19910111 (199113)*
EP 421577 A 19910410 (199115)
R: AT BE CH DE ES FR GB GR IT LI LU NL SE
JP 03063232 A 19910319 (199117)
US 5232707 A 19930803 (199332) 8p
ADT CA 2020755 A CA 1990-2020755 19900709; EP 421577 A EP 1990-307543 19900710; JP 03063232 A JP 1990-181368 19900709; US 5232707 A Cont of US 1989-377648 19890710, US 1991-759803 19910913
PRAI US 1989-377648 19890710
AB CA 2020755 A UPAB: 19930928
A polymer-drug microcapsule compsn., in which the drug is at least one hormonally active water-soluble polypeptide, is contacted with a pressurised gas for a time sufficient to mobilisee and hereby extract from the microcapsules at least some of any residual solvents contained in them, and then the gas and such residuel solvents are removed.

As the pressurised gas there may be used CO2 alone or mixts. of CO2 with C3H8, C9H12 or C7H16. The CO2 pressure may be in the range 100-300 psi, pref. 110-250 psi; or when in the presence of a gaseous or liquid pressurizewd pressurised alkane, in the range 100-500 psi, pref. 110-400 psi. The pressure is pref. constant.

USE/ADVANTAGE - The compsn. may e.g. be that described in U.S. Pat. Number 4,675,189 for **sustained release** of a luteinising hormone-**releasing hormone** (LHRH) analogue. While the presence of residual solvents in such a compsn. is not believed to render the compsn. unsuitable or unsafe for human use, it is describe to reduce the concentration. @(26pp Dwg.No.0/0

L14 ANSWER 22 OF 25 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
AN 1988-297312 [42] WPIDS

DNC C1988-131971
TI Preparation of **glycolic** acid-L-**lactic** acid complex - by melting, dispersing hormone in **copolymer** at room temperature, opt. agitating etc..
DC A96 B04 C03
PA (JAAT) JAPAN ATOMIC ENERGY RES INST; (TAGI-N) TAGI KAGAKU KK
CYC 1
PI JP 63218632 A 19880912 (198842)* 11p
ADT JP 63218632 A JP 1987-51777 19870306
PRAI JP 1987-51777 19870306
AB JP 63218632 A UPAB: 19930923
Sustained releasing complex contains **hormone**, in which use is made of **copolymer** of **glycolic** acid with **lactic** acid, having molecular weight of 200-5000 pref. 30-70% L-**lactic** acid. Preparation of the complex comprises melting or dispersing hormone in **copolymer** of **glycolic** acid with L-**lactic** acid at room temperature to 150 deg.C. Also claimed is preparation of the complex where hormone is melted or dispersed in **copolymer** of **glycolic** acid with L-**lactic** acid, followed by well agitation, and the resultant is moulded at room temperature to 150 deg.C under normal pressure to 1000 kg/cm2 and the resultant is then introduced in a teflon tube cylinder.
ADVANTAGE - **Sustained release** preparation of hormones can be obtd. without reduction of hormone activity during the preparation The hormone includes steroid hormones, e.g. hydroxidase, isomelase, hydrogenase, androgen, estrogen, gluco corticoid and mineral acoricoid, peptide hormones e.g. thyroid stimulating hormone **releasing hormone**, luteinising **hormone**, adrenal cortex stimulating hormone, prolactin, thyroid stimulating hormone and insulin, cathechol amine, insect hormones, vegetable hormones, etc.
0/0

L14 ANSWER 23 OF 25 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
AN 1988-051483 [08] WPIDS
DNC C1988-022789
TI Polymer microcapsules of thyrotropin-**releasing hormone** or analogue - prepared by forming water-oil emulsion in polymer solution, dispersing in external aqueous phase and evaporating solvent.
DC A96 B03
IN HEYA, T; OGAWA, Y; OKADA, H; OGAWA, K
PA (TAKE) TAKEDA CHEM IND LTD
CYC 19
PI EP 256726 A 19880224 (198808)* EN 11p
R: AT BE CH DE ES FR GB GR IT LI LU NL SE
JP 63233926 A 19880929 (198845)
NO 8800502 A 19890206 (198911)
FI 8800511 A 19890111 (198915)
HU 52700 T 19900828 (199039)#
CA 1300011 C 19920505 (199223)
EP 256726 B1 19921007 (199241) EN 15p
R: AT BE CH DE ES FR GB GR IT LI LU NL SE
DE 3782117 G 19921112 (199247)
JP 2526589 B2 19960821 (199638) 8p
US 5652220 A 19970729 (199736) 6p
ADT EP 256726 A EP 1987-306794 19870731; JP 63233926 A JP 1987-173523 19870710; CA 1300011 C CA 1987-543516 19870731; EP 256726 B1 EP 1987-306794 19870731; DE 3782117 G DE 1987-3782117 19870731, EP 1987-306794 19870731; JP 2526589 B2 JP 1987-173523 19870710; US 5652220 A Cont of US 1987-73741 19870715, Cont of US 1989-332373 19890403, Cont of US 1992-882255 19920508, Cont of US 1993-62144 19930517, US 1995-416518

19950404
FDT DE 3782117 G Based on EP 256726; JP 2526589 B2 Previous Publ. JP 63233926
PRAI JP 1987-173523 19870710; JP 1986-187467 19860808
AB EP 256726 A UPAB: 19970502
A microcapsule comprises a polymer and 2-15 weight%, based on polymer, of thyrotropin - **releasing hormone** (TRH) or its analogue or salt with a weak acid of pKa not less than 4.0. Preparation of the microcapsule comprises forming a W/O emulsion of an oil phase containing polymer and an aqueous phase containing 2-15 weight%, based on polymer, of TRH or analogue or salt, mixing the emulsion with an aqueous solution of a dispersing agent to form a W/O/W emulsion, then distilling off the oil phase solvent.
USE/ADVANTAGE - Used for **sustained release** of the TRH or analogues from implants, injections, oral or nasal prepns., rectal, uretural or vaginal suppositories, etc., for admin. to humans and animals. Doses are e.g. 0.1-100, pref. 0.2-50 mg/kg, in a volume of e.g. 0.1-5, pref. 0.2-3 ml for injection.
Dwg./0

L14 ANSWER 24 OF 25 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
AN 1986-311723 [48] WPIDS
CR 1985-100425 [17]; 1985-106422 [18]; 1985-111858 [19]
DNC C1986-135024
TI Slow release preparation of growth promoting or bony metabolism peptide - with collagen, gelatin and/or albumin as carrier protein.
DC B04 B05 B07 C03 P32
IN FUJIOKA, K; SATO, S; TAKADA, Y; YAMAHIRA, Y
PA (SUMU) SUMITOMO PHARM CO LTD
CYC 5
PI AU 8655983 A 19861016 (198648)* 18p
JP 61236729 A 19861022 (198649)
US 4774091 A 19880927 (198841)
US 5021241 A 19910604 (199138)
JP 06057658 B2 19940803 (199429)
US 5385738 A 19950131 (199511) 7p
ADT AU 8655983 A AU 1986-55983 19860411; JP 61236729 A JP 1985-77250 19850411; US 4774091 A US 1986-846193 19860331; US 5021241 A US 1988-187443 19880428; JP 06057658 B2 JP 1985-77250 19850411; US 5385738 A CIP of US 1984-660044 19841012, Cont of US 1986-849968 19860410, Cont of US 1990-488531 19900228, US 1992-844929 19920304
FDT JP 06057658 B2 Based on JP 61236729
PRAI JP 1983-193064 19831014; JP 1983-206226 19831101; JP 1983-236994 19831214; JP 1983-236995 19831214; JP 1983-236996 19831214; JP 1985-77250 19850411; JP 1983-220452 19831121
AB AU 8655983 A UPAB: 19950508
Sustained release preparation comprises a peptide (I) with growth promoting activity or activity relating to bony metabolism, together with a carrier protein from collagen, gelatin and/or albumin. Pref. (I) is growth hormone (GH), growth hormone **releasing factor** (GRF) or somatomedin (SM) as growth promotor, or calcitonin as bony metabolism active agent.
USE/ADVANTAGE - Useful for treating dwarfism in humans, promoting growth in livestock, promoting lactation, etc. **Release** can be **sustained**, avoiding the need for repeated admin.
Dwg.0/1
Dwg.0/1

L14 ANSWER 25 OF 25 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
AN 1986-306804 [47] WPIDS
DNC C1986-132841

TI Biodegradable polymer with low free acid content - and used in drug microencapsulation is e.g. hydroxy-acid ester or poly cyano-acrylic -ester.

DC A96 B07

IN MIYAGAWA, T; OGAWA, Y; OKADA, H; YAMAMOTO, M

PA (TAKE) TAKEDA CHEM IND LTD; (WAKP) WAKO PURE CHEM INDS LTD; (WAKP) WAKO PURE CHEM IND LTD

CYC 15

PI EP 202065 A 19861120 (198647)* EN 23p
R: AT BE CH DE FR GB IT LI LU NL SE
JP 62054760 A 19870310 (198715)
HU 43488 T 19871130 (198751)
US 4728721 A 19880301 (198812)
US 4849228 A 19890718 (198936)
CA 1262005 A 19890926 (198945)
EP 202065 B1 19930407 (199314) EN 12p
R: AT BE CH DE FR GB IT LI LU NL SE
DE 3688213 G 19930513 (199320)
JP 08169818 A 19960702 (199636) 6p
JP 2551756 B2 19961106 (199649) 6p
JP 2660401 B2 19971008 (199745) 6p

ADT EP 202065 A EP 1986-303417 19860506; JP 62054760 A JP 1986-94167 19860423; US 4728721 A US 1986-853040 19860501; US 4849228 A US 1987-117618 19871106; EP 202065 B1 EP 1986-303417 19860506; DE 3688213 G DE 1986-3688213 19860506, EP 1986-303417 19860506; JP 08169818 A Div ex JP 1986-94167 19860423, JP 1995-232297 19860423; JP 2551756 B2 JP 1986-94167 19860423; JP 2660401 B2 Div ex JP 1986-94167 19860423, JP 1995-232297 19860423

FDT DE 3688213 G Based on EP 202065; JP 2551756 B2 Previous Publ. JP 62054760; JP 2660401 B2 Previous Publ. JP 08169818

PRAI JP 1985-97617 19850507; JP 1986-94167 19860423

AB EP 202065 A UPAB: 19930922
Biodegradable high molecular polymer (I) has the content of water-soluble low molecular cpds. (II), calculated on the assumption that (II) are monobasic acids, is below 0.01 mole/100 g (I).

Microcapsule for injectable **sustained release** is also claimed and contains an effective amount of an ingredient (III) and (I) (as above) as excipient. Preparation of the microcapsule is also claimed and comprises: preparing a w/o emulsion with a solution of (III) as aqueous phase and a solution of (I) as oil phase; dispersing the emulsion in an aqueous phase to give a (W/O)/W emulsion; and subjecting the emulsion to a 3rd aqueous phase to give a (W/O)/W ternary phase emulsion from which the solvent in the oil phase is then desorbed.

(I) are e.g. hydroxyacid polyesters (polyactic acid, **polyglycolic** acid), polycyanoacrylic acid esters, polyhydroxybutyric acid, poly-gamma-caprolactone, polyorthoesters and polyorthocarbonates.

USE/ADVANTAGE - (I), and compsns. containing them, have good stability towards ageing, by using (I), increased rates of drug incorporation of (III) during microencapsulation are attained; and the microcapsules show reduced initial burst of release of (III) so that constant release over a prolonged period is observed. Microcapsules obtd. are esp.useful for delivery of water-soluble peptides, e.g. LHRH-like peptides, thyroid hormone **releasing hormone**-like **peptides**, etc.

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     (FILE 'REGISTRY' ENTERED AT 12:41:52 ON 01 MAR 2004)
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               ACT PROVISO/A
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L5            1 S 34346-01-5
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     FILE 'CAPLUS' ENTERED AT 12:46:59 ON 01 MAR 2004
L8         1693 S L5
L9         5080 S L6 OR L7
L10        6087 S L8 OR L9
L11         106 S GNRH II
L12         196 S GONADOTROPIN RELEAS? HORMONE (2W) II
L13         114 S GNRH (2W) II
L14         269 S L13 OR L12
L15         269 S L11-L13
L16           1 S L15 AND L10
L17        8570 S GNRH OR GONADOTROPIN RELEAS? (L) HORMONE
L18           8 S L17 AND L10

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L19           1 S 9034-40-6

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L20       15031 S L19
L21          73 S L20 AND L10
L22       28764 S (TIM? OR CONTROL? OR SUSTAIN? ) (L) RELEAS?
L23          56 S L21 AND L22

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               E GONADOTROPIN-RELEASING /CN

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L24           8 S L16 OR L18
L25          52 S L23 NOT L24
L26          46 S L25 AND P/DT
               SET SFIELD BI
L27       11711 S GNRH OR GNRHII OR GONADOTROPIN RELEAS? (2W) (FACTOR OR HORMON
L28           0 S L27 AND L26
L29           4 S L23 AND L27
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Property values tagged with IC are from the ZIC/VINITI data file
provided by InfoChem.

STRUCTURE FILE UPDATES:   29 FEB 2004  HIGHEST RN 656221-41-9
DICTIONARY FILE UPDATES:  29 FEB 2004  HIGHEST RN 656221-41-9

TSCA INFORMATION NOW CURRENT THROUGH JULY 14, 2003

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

Crossover limits have been increased.  See HELP CROSSOVER for details.

Experimental and calculated property data are now available. For more
information enter HELP PROP at an arrow prompt in the file or refer
to the file summary sheet on the web at:
http://www.cas.org/ONLINE/DBSS/registryss.html

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L3   ANSWER 1 OF 5  REGISTRY  COPYRIGHT 2004 ACS on STN
RN   306967-56-6  REGISTRY
CN   Luteinizing hormone-releasing factor II [11-glycine,12-lysine] (chicken
     tetramer) (9CI)  (CA INDEX NAME)
FS   PROTEIN SEQUENCE
SQL  60

SEQ3     1 Met-Gly-Lys-Arg-Glu-His-Trp-Ser-His-Gly-
                         === === === === === ===
        11 Trp-Tyr-Pro-Gly-Gly-Lys-Arg-Glu-His-Trp-
           === === === ===              === === ===
        21 Ser-His-Gly-Trp-Tyr-Pro-Gly-Gly-Lys-Arg-
           === === === === === === ===
        31 Glu-His-Trp-Ser-His-Gly-Trp-Tyr-Pro-Gly-
           === === === === === === === === === ===
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                     === === === === === === ===
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           === === ===
HITS AT:   5-14, 18-27, 31-40, 44-53


**RELATED SEQUENCES AVAILABLE WITH SEQLINK**
MF   C338 H459 N105 O79 S
CI   MAN
SR   CA
LC   STN Files:   CA, CAPLUS
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1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L3 ANSWER 2 OF 5 REGISTRY COPYRIGHT 2004 ACS on STN
RN 262434-45-7 REGISTRY
CN Luteinizing hormone-releasing factor II (synthetic chicken peptide-linker multimer) (9CI) (CA INDEX NAME)
OTHER NAMES:
CN 5: PN: WO0017336 FIG: 9 claimed protein
FS PROTEIN SEQUENCE
SQL 60

PATENT ANNOTATIONS (PNTE):

Sequence Source	Patent Reference
Not Given	WO2000017336 claimed FIG 9

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    === === === === === === ===
 31 Glu-His-Trp-Ser-His-Gly-Trp-Tyr-Pro-Gly-
    === === === === === === === === === ===
 41 Gly-Lys-Arg-Glu-His-Trp-Ser-His-Gly-Trp-
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 51 Tyr-Pro-Gly-Gly-Lys-Arg-Leu-Glu-Lys-Leu
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HITS AT: 5-14, 18-27, 31-40, 44-53

RELATED SEQUENCES AVAILABLE WITH SEQLINK
MF C338 H459 N105 O79 S
CI MAN
SR CA
LC STN Files: CA, CAPLUS
1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L3 ANSWER 3 OF 5 REGISTRY COPYRIGHT 2004 ACS on STN
RN 261962-22-5 REGISTRY
CN L-Lysine, L-α-glutamyl-L-histidyl-L-tryptophyl-L-seryl-L-histidylglycyl-L-tryptophyl-L-tyrosyl-L-prolylglycylglycyl- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN 8: PN: WO0017336 PAGE: 15 claimed sequence
FS PROTEIN SEQUENCE; STEREOSEARCH
SQL 12

PATENT ANNOTATIONS (PNTE):

Sequence Source	Patent Reference
Not Given	WO2000017336 claimed PAGE

|15

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HITS AT: 1-10

MF C68 H85 N19 O17
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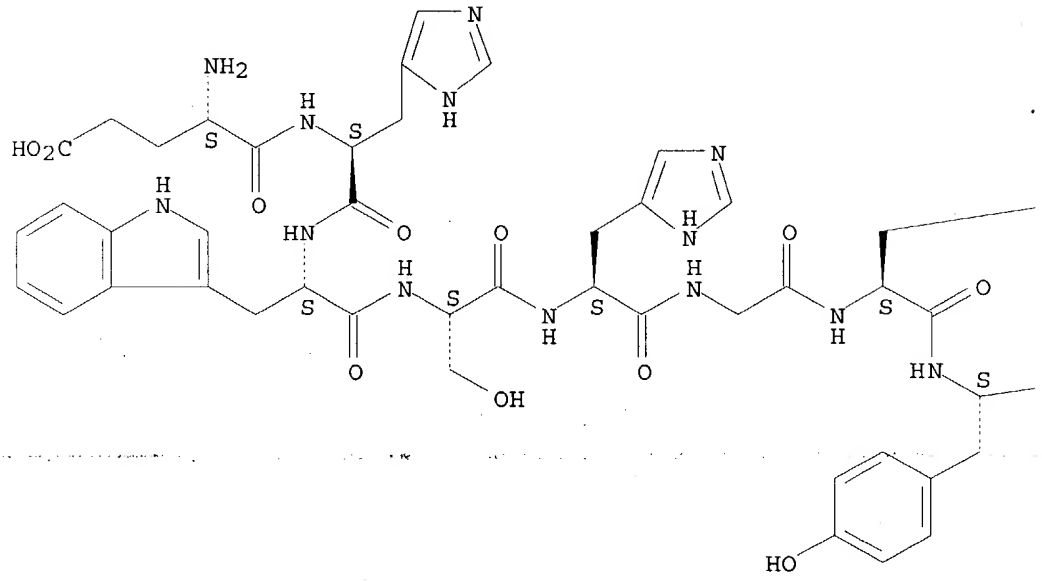
LC STN Files: CA, CAPLUS

Absolute stereochemistry.

PAGE 1-A



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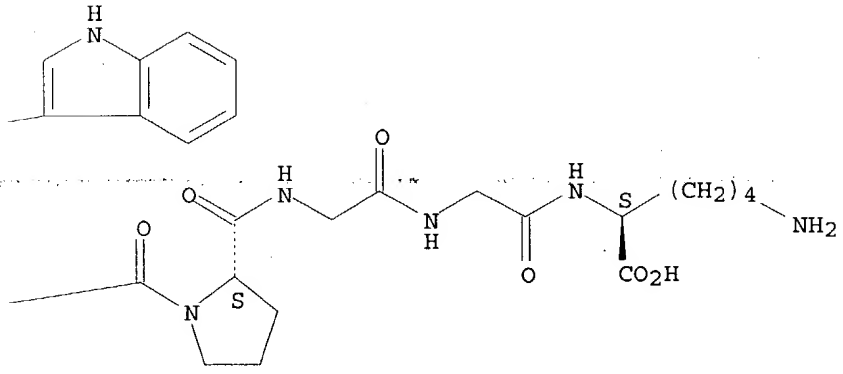

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RN 261962-21-4 REGISTRY
CN L-Arginine, L-α-glutamyl-L-lysyl-L-arginyl-L-α-glutamyl-L-histidyl-L-tryptophyl-L-seryl-L-histidylglycyl-L-tryptophyl-L-tyrosyl-L-prolylglycylglycyl-L-lysyl- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN 3: PN: WO0017336 FIGURE: 2 claimed sequence
FS PROTEIN SEQUENCE; STEREOSEARCH
SQL 16

PATENT ANNOTATIONS (PNTE):

Sequence Source	Patent Reference
Not Given	WO2000017336 claimed FIGURE 2

SEQ3 1 Glu-Lys-Arg-Glu-His-Trp-Ser-His-Gly-Trp-
=== === === === === === === === ===
11 Tyr-Pro-Gly-Gly-Lys-Arg
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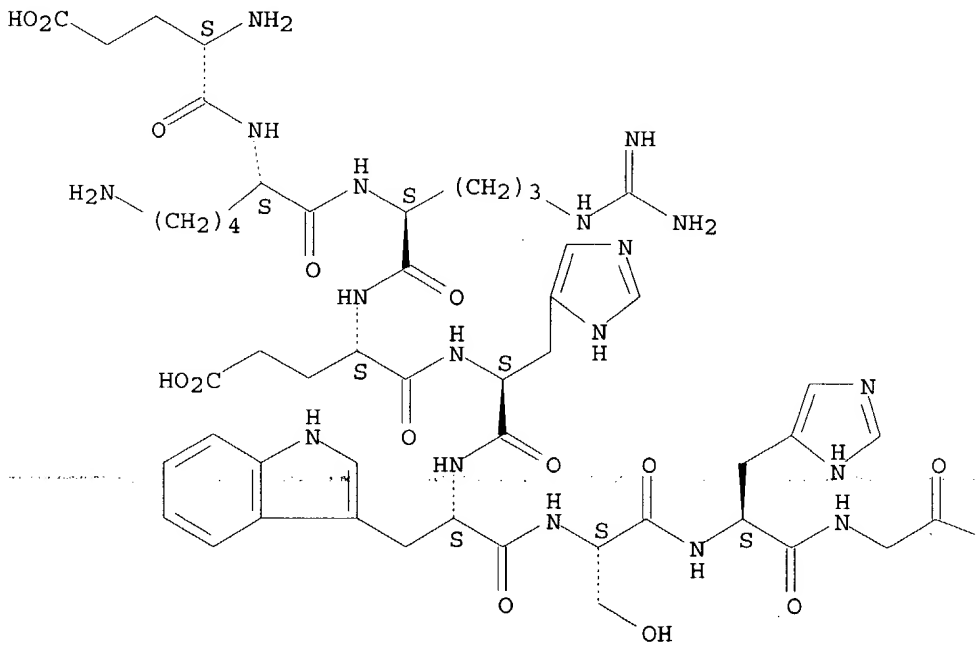
HITS AT: 4-13

MF C91 H128 N30 O23
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.

PAGE 1-A



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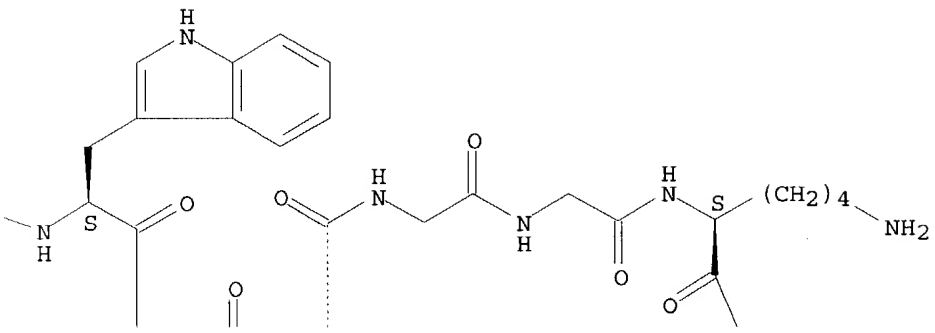

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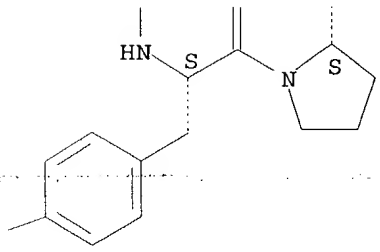
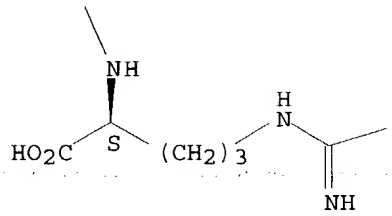
PAGE 2-B





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1 REFERENCES IN FILE CA (1907 TO DATE)
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1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L3 ANSWER 5 OF 5 REGISTRY COPYRIGHT 2004 ACS on STN
RN 261962-20-3 REGISTRY
CN Glycine, L-α-glutamyl-L-histidyl-L-tryptophyl-L-seryl-L-histidylglycyl-L-tryptophyl-L-tyrosyl-L-prolyl- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN 12: PN: WO03051272 SEQID: 12 claimed sequence
CN 133: PN: WO00069900 SEQID: 136 unclaimed sequence
CN 2: PN: WO00017336 FIGURE: 2 claimed sequence
CN 7: PN: WO00032218 SEQID: 6 unclaimed sequence
FS PROTEIN SEQUENCE; STEREOSEARCH
SQL 10

PATENT ANNOTATIONS (PNTE):

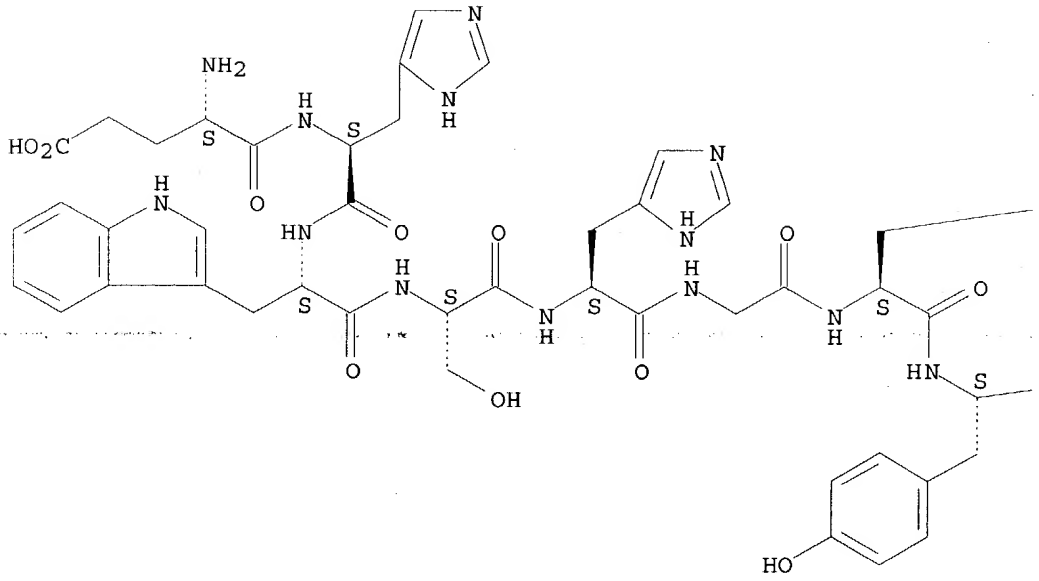
Sequence Source	Patent Reference
Not Given	WO2000017336 claimed FIGURE 2
	WO2000032218 unclaimed SEQID 6
	WO2000069900 unclaimed SEQID 136

SEQ3 1 Glu-His-Trp-Ser-His-Gly-Trp-Tyr-Pro-Gly
=== === === === === === === === === ===
HITS AT: 1-10

MF C60 H70 N16 O15
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER

Absolute stereochemistry.

PAGE 1-A



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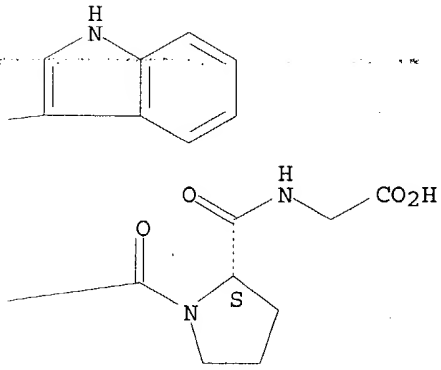

4 REFERENCES IN FILE CA (1907 TO DATE)
4 REFERENCES IN FILE CAPLUS (1907 TO DATE)

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FILE COVERS 1907 - 1 Mar 2004 VOL 140 ISS 10
FILE LAST UPDATED: 29 Feb 2004 (20040229/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

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L2          152 SEA FILE=REGISTRY ABB=ON  PLU=ON  EHWS[HY]G[WL][YR]PG/SQSP
L3            5 SEA FILE=REGISTRY ABB=ON  PLU=ON  L2 NOT L1
L4            5 SEA FILE=CAPLUS ABB=ON  PLU=ON  L3


=> d .ca l4 1-5

L4   ANSWER 1 OF 5  CAPLUS  COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER:         2003:490972  CAPLUS
DOCUMENT NUMBER:          139:67778
TITLE:                    Gonadotrophin releasing hormone I and II, antibodies,
                          anti-receptor antibodies and polynucleotides for
                          modulation of T-cell activity, adhesion, migration and
                          extravasation
INVENTOR(S):              Levite, Mia; Koch, Yitzhak
PATENT ASSIGNEE(S):       Yeda Research and Development Co., Ltd., Israel
SOURCE:                   PCT Int. Appl., 177 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.          KIND  DATE          APPLICATION NO.  DATE
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     WO 2003051272        A2   20030626      WO 2002-IL1014   20021217
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             FI, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG,
             KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW,
             MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SK,
             SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM,
             ZW, AM, AZ, BY
         RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG,
             CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL,
             PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML,
             MR, NE, SN, TD, TG
PRIORITY APPLN. INFO.:                    IL 2001-147138   A  20011217
AB   Methods and compns. comprising gonadotropin releasing hormone GnRH-I and
     GnRH-II, GnRH-I and GnRH-II antibodies, anti-receptor antibodies,
     polynucleotide constructs and GnRH-I and GnRH-II analogs for immune
     enhancement and suppression, prevention and treatment of diseases and
```

conditions characterized by abnormal T-cell activity, treatment of viral and prion-related diseases, and treatment of T-cell related neoplastic diseases are disclosed.

IC ICM A61K

CC 15-3 (Immunochemistry)
Section cross-reference(s): 2, 3, 9

IT 9034-40-6P, Gonadotropin releasing hormone 60556-70-9P 102714-10-3P, Gonadotropin releasing hormone II 125804-99-1P, Gonadotropin releasing hormone I 140743-84-6P, GenBank X15215 142552-12-3P 168691-70-1P 183127-68-6P **261962-20-3P** 309244-23-3P 309244-34-6P 309244-35-7P 392041-99-5P, GenBank AF36329 548428-34-8P 548428-35-9P 548428-36-0P 548428-37-1P 548428-38-2P 548428-39-3P 548428-40-6P 548428-41-7P 548428-42-8P 548428-43-9P 548428-44-0P 548428-45-1P 548428-46-2P 548428-47-3P 548525-23-1DP, substituted analogs 548525-24-2DP, substituted analogs
RL: BPN (Biosynthetic preparation); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(gonadotropin releasing hormone I and II, antibodies, anti-receptor antibodies and polynucleotides for modulation of T-cell activity, adhesion, migration and extravasation)

L4 ANSWER 2 OF 5 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:824291 CAPLUS
DOCUMENT NUMBER: 134:21425
TITLE: Protection of endogenous therapeutic peptides from peptidase activity through conjugation to blood components
INVENTOR(S): Bridon, Dominique P.; Ezrin, Alan M.; Milner, Peter G.; Holmes, Darren L.; Thibaudeau, Karen
PATENT ASSIGNEE(S): Conjuchem, Inc., Can.
SOURCE: PCT Int. Appl., 733 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000069900	A2	20001123	WO 2000-US13576	20000517
WO 2000069900	A3	20010215		
WO 2000069900	C2	20020704		

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RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

WO 2000070665	A2	20001123	WO 2000-IB763	20000517
WO 2000070665	A3	20010419		

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EP 1105409	A2	20010613	EP 2000-936023	20000517
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JP 2003508350	T2	20030304	JP 2000-618316	20000517
AU 765753	B2	20030925	AU 2000-51393	20000517
US 6514500	B1	20030204	US 2000-657332	20000907
ZA 2001006676	A	20020719	ZA 2001-6676	20010814
ZA 2001009110	A	20020613	ZA 2001-9110	20011105
US 2003108567	A1	20030612	US 2002-287892	20021104
US 2003108568	A1	20030612	US 2002-288340	20021104

PRIORITY APPLN. INFO.:

US 1999-134406P	P	19990517
US 1999-153406P	P	19990910
US 1999-159783P	P	19991015
EP 2000-932570	A3	20000517
WO 2000-IB763	W	20000517
WO 2000-US13576	W	20000517
US 2000-657332	A3	20000907

AB A method for protecting a peptide from peptidase activity in vivo, the peptide being composed of between 2 and 50 amino acids and having a C-terminus and an N-terminus and a C-terminus amino acid and an N-terminus amino acid is described. In the first step of the method, the peptide is modified by attaching a reactive group to the C-terminus amino acid, to the N-terminus amino acid, or to an amino acid located between the N-terminus and the C-terminus, such that the modified peptide is capable of forming a covalent bond in vivo with a reactive functionality on a blood component. The solid phase peptide synthesis of a number of derivs. with 3-maleimidopropionic acid (3-MPA) is described. In the next step, a covalent bond is formed between the reactive group and a reactive functionality on a blood component to form a peptide-blood component conjugate, thereby protecting said peptide from peptidase activity. The final step of the method involves the analyzing of the stability of the peptide-blood component conjugate to assess the protection of the peptide from peptidase activity. Thus, the percentage of a K5 kringle peptide (Pro-Arg-Lys-Leu-Tyr-Asp-Lys-NH2) conjugated to human serum albumin via MPA remained relatively constant through a 24-h plasma assay in contrast to unmodified K5 which decreased to 9% of the original amount of K5 in only 4 h in plasma.

IC ICM C07K014-00

CC 63-3 (Pharmaceuticals)
Section cross-reference(s): 34

IT 158561-91-2 158622-13-0 158879-51-7 158884-65-2 159623-45-7 159829-06-8 159964-40-6 160112-12-9 160187-72-4 160210-00-4 160507-34-6 161206-81-1 161748-27-2 162929-64-8 165338-06-7 166546-45-8 166546-72-1 166824-48-2, 1-24-Neuropeptide Y (human) 167114-91-2 168633-88-3 169228-94-8, Luteinizing hormone-releasing factor (Sparus auratus) 170032-25-4 170032-27-6 170713-75-4, Orphanin FQ (swine) 171089-50-2 171876-68-9 172838-27-6, Protegrin 1 (reduced) 172998-24-2, 16-36-Buforin I 174643-45-9 175799-54-9 176260-88-1 176843-96-2 176843-98-4 178629-74-8 182374-54-5 182804-15-5 183476-25-7 183788-96-7 185391-83-7 185391-85-9

185458-37-1 185805-61-2 185805-76-9 186253-19-0 187345-00-2
188405-30-3 188427-41-0 188954-16-7 189224-35-9 190436-05-6
191280-45-2 191867-98-8 191919-78-5 191919-81-0 191919-84-3
192432-73-8 195832-30-5 198276-46-9 198277-98-4 198333-83-4
198481-81-1 198483-36-2 198483-37-3 198542-00-6 198623-87-9,
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256230-32-7 256230-34-9 256933-30-9 259111-03-0 259243-44-2
260060-44-4 260542-01-6 **261962-20-3** 263006-62-8
280748-65-4 282714-14-1 287376-78-7 292631-06-2 299161-39-0
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309244-64-2 309244-65-3 309244-66-4 309244-67-5 309244-68-6
309244-69-7 309244-70-0 309244-71-1 309244-72-2 309244-87-9
309244-88-0
RL: PRP (Properties)
(unclaimed sequence; protection of endogenous therapeutic peptides from peptidase activity through conjugation to blood components)

L4 ANSWER 3 OF 5 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:383955 CAPLUS
DOCUMENT NUMBER: 133:39671
TITLE: Controlled release formulation comprising gonadotropin-releasing hormone-II
INVENTOR(S): Qi, Steve; Akinsanya, Karen; Hayward, Amanda
PATENT ASSIGNEE(S): Ferring Bv, Neth.
SOURCE: PCT Int. Appl., 25 pp. 371
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000032218	A1	20000608	WO 1999-GB4045	19991202
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
GB 2344287	A1	20000607	GB 1998-26662	19981203
BR 9915943	A	20010821	BR 1999-15943	19991202
EP 1140133	A1	20011010	EP 1999-958357	19991202
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
EE 200100293	A	20020815	EE 2001-293	19991202
NZ 511984	A	20021126	NZ 1999-511984	19991202
NO 2001002636	A	20010712	NO 2001-2636	20010529
ZA 2001004530	A	20020604	ZA 2001-4530	20010601
HR 2001000421	A1	20020630	HR 2001-421	20010601

PRIORITY APPLN. INFO.: GB 1998-26662 A 19981203
WO 1999-GB4045 W 19991202

AB A pharmaceutical formulation is disclosed for the controlled release of a therapeutic peptide or a salt thereof, which peptide has the sequence pyroGlu-His-Trp-Ser-Xaa1-Gly-Xaa2-Xaa3-Pro-Gly-NH2 wherein Xaa1 is His or Tyr, Xaa2 is Trp or Leu, and Xaa3 is Tyr or Arg, provided that when Xaa1 is Tyr and Xaa2 is Leu, then Xaa3 is not Arg, and which formulation further comprises a pharmaceutically acceptable biodegradable polymer. The formulation can be used for treating bone and prostate disorders.

IC ICM A61K038-09
ICS A61K047-34

CC 6-3 (General Biochemistry)
Section cross-reference(s): 2

IT 60556-70-9 **261962-20-3**
RL: PRP (Properties)
(unclaimed sequence; controlled release formulation comprising gonadotropin-releasing hormone-II)

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 4 OF 5 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2000:298463 CAPLUS
DOCUMENT NUMBER: 134:1126
TITLE: A novel technique for the effective production of short peptide analogs from concatemeric short peptide multimers
AUTHOR(S): Lee, Sang Jun; Lee, Jong Hee; Jin, Hyun Joo; Lee, Jeong Ho; Ryu, Ho Young; Kim, Yoon; Kong, In Soo; Kim, Kyu Won
CORPORATE SOURCE: Biotechnology Division, National Fisheries Research and Development Institute, Pusan, 619-900, S. Korea
SOURCE: Molecules and Cells (2000), 10(2), 236-240
CODEN: MOCEEK; ISSN: 1016-8478
PUBLISHER: Springer-Verlag Singapore Pte. Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB We designed a basic unit of the modified chicken gonadotropin releasing hormone II (cGnRH-II) peptide containing a trypsin cleavable linker peptide at

both ends of the original peptide. We made a synthetic DNA coding for the modified cGnRH-II peptide with asym. and complementary cohesive ends of linker nucleotides. A tandemly repeated DNA cassette for the expression of concatemeric short peptide multimers was constructed by ligating the basic units. The expressed peptide multimers were purified and subject to amino-terminal sequence anal., which displayed the amino acid sequences expected from the designed nucleotides of the expression cassette. The monomeric cGnRH-II peptide analogs were generated after trypsin digestion. The present results showed that the technique developed for the production of the concatemeric peptide multimers with cleavable linker peptides can be generally applicable to the production of short peptide analogs.

CC 3-2 (Biochemical Genetics)
Section cross-reference(s): 2

IT **306967-56-6P**
RL: BPN (Biosynthetic preparation); PRP (Properties); BIOL (Biological study); PREP (Preparation)
(amino acid sequence; novel technique for effective production of short peptide analogs from concatemeric short peptide multimers)

IT **261962-22-5P**
RL: BPN (Biosynthetic preparation); PUR (Purification or recovery); BIOL (Biological study); PREP (Preparation)
(novel technique for effective production of short peptide analogs from concatemeric short peptide multimers)

REFERENCE COUNT: 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 5 OF 5 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:210341 CAPLUS
DOCUMENT NUMBER: 132:247155
TITLE: DNA cassette encoding a multimer of a biologically active peptide and a cleavable linker attached thereto and process for preparing the biologically active peptide
INVENTOR(S): Lee, Sang Jun
PATENT ASSIGNEE(S): S. Korea
SOURCE: PCT Int. Appl., 32 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000017336	A1	20000330	WO 1999-KR559	19990917
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9957626	A1	20000410	AU 1999-57626	19990917
KR 2000023309	A	20000425	KR 1999-40433	19990920

PRIORITY APPLN. INFO.: KR 1998-38835 A 19980919
WO 1999-KR559 W 19990917

AB A biol. active peptide is prepared by: (a) preparing an expression vector comprising a DNA cassette containing two or more tandem repeating units of a

nucleotide sequence encoding a biol. active peptide and a linker peptide attached thereto, the linker peptide being cleavable by a protease or a chemical agent; (b) transforming a microorganism with the expression vector; (c) culturing the transformed microorganism to produce a multimeric peptide expressed by the DNA cassette; (d) recovering and digesting the multimeric peptide with the protease or the chemical agent to obtain the biol. active peptide or an analog thereof carrying one or more amino acid residues originating from the linker peptide. Thus, a trypsin-digestible linker peptide represented by Gly-Lys-Arg was designed. Based on the amino acid sequence of chicken gonadotropin-releasing hormone II (cGnRH-II) and the linker peptide, a basic peptide unit was designed comprising Gly-Lys-Arg-Glu-His-Trp-Ser-His-Gly-Trp-Tyr-Pro-Gly-Gly-Lys-Arg. A DNA fragment was deduced to match linker-cGNRH-II-linker using the standard genetic codes, and the DNA cassette inserted into an expression vector for expression in Escherichia coli.

IC ICM C12N015-00
ICS C12N015-12; C12N015-62; C12N001-21; C12N001-21; C12R001-19

CC 3-2 (Biochemical Genetics)
Section cross-reference(s): 2

IT **261962-22-5P**
RL: BMF (Bioindustrial manufacture); BIOL (Biological study); PREP (Preparation)
(DNA cassette encoding a multimer of a biol. active peptide and a cleavable linker attached thereto and process for preparing the biol. active peptide)

IT **262434-45-7P**
RL: BMF (Bioindustrial manufacture); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PREP (Preparation); PROC (Process)
(amino acid sequence; DNA cassette encoding a multimer of a biol. active peptide and a cleavable linker attached thereto and process for preparing the biol. active peptide)

IT **261962-20-3 261962-21-4D**, multimers
RL: BPR (Biological process); BSU (Biological study, unclassified); BUU (Biological use, unclassified); BIOL (Biological study); PROC (Process); USES (Uses)
(cGN-RH-II peptide; DNA cassette encoding a multimer of a biol. active peptide and a cleavable linker attached thereto and process for preparing the biol. active peptide)

REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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